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THE PROBLEM OF POSTWAR SURGICAL TRAINING FOR RETURNING MEDICAL OFFICERS*

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THE subject of postwar training and rehabilitation of medical officers, now active in the Army, the Navy, the Marines and the Public Health Service in this country and on every continent and ocean, is closely linked with the plan and philosophy of the armed forces as they are functioning in this global war.

The experience of this country in the last war in helping to win it but sharing an even greater responsibility in losing the peace was a sobering one. All but the blind isolationists realized after the convincing evidences of the power and insane ambitions of Germany in Europe and the increasing encroachments of Japan in the Pacific that we were facing an inevitable conflict. But we were fortunate in having time to prepare for the war by getting our facilities mobilized during the early days of lend-lease, and the Nation was psychologically prepared for the draft and an all-out war effort before Pearl Harbor.

There was none of the flag-waving and impatient enthusiasm on the part of the citizenry and youth to enter this war that were evident in the last one. The young men and women faced the inevitable with a seriousness and a conviction that those of the World War I generation, not they, were responsible for the present situation in so deplorably losing the opportunities presented for winning the peace.

One of the outstanding differences between the conduct of the last war and the present one is the special training of the men in all branches of the service for their jobs. Because the armed forces are engaged in all parts of the world they have been given more careful selected training and more initiative than in the last war. The rapid development of fighting in the air, on the ground and on and under the ocean has produced weapons, machines and physical means of communication and detection never conceived of in previous wars. This has resulted in the training and bringing out of initiative in literally millions of young people, male and female, that will demand expression, as soon as the war is over, in work and occupation that cannot be denied.

The last war, by and large, provided a type of experience in trench and stabilized warfare that was directly opposed to the later demands of civilian life. This war, because of its global distribution and its mobile character, is providing countless experiences that can be translated into success in civil life. Training programs and a more intelligent evaluation of previous experience, aptitudes and latent abilities have resulted in an incomparably more intelligent and efficient Army and Navy than we have ever had before, and a body of men and women who, because of this experience, will rightly demand a proper place in life on their return.

In a recent visit to our forces in Great Britain and North Africa I was impressed by the general concern of the soldiers and officers over four possibilities. First was the fear that war weariness and complacency at home would lead to a premature cessation of hostilities, — in which they were doing the fighting and dying, — which would again result in losing the peace. Second was a bitter resentment and anger over the conflict between capital and labor, resulting in strikes and interference with the war effort: the coal strike was threatening, and Lewis was more hated than Hitler. Third was apprehension regarding postwar opportunity and employment. Last was uncertainty regarding the utilization of their newly acquired experience and the means of further training to perfect themselves in these fields.

Just what will the answer be to this group of ten to thirteen million men and women as they return to civilian life? Do American businessmen, industrial leaders and professional groups believe that a World War I ideology and a Versailles Treaty attitude will be able to cope with this problem and provide leadership acceptable to these new veterans

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of World War II? If so, we may be sure of a fusion of these millions of men and women and their families, resentful of such an attitude and ready to follow radical leadership into the most powerful pressure group this country has ever known, with a block of votes that will make any Congress dance to any tune.

What has been said about the men in the service in general applies equally to the medical officers in the armed forces. But they have additional problems peculiar to their profession. The older group have left practices of various kinds of work and compensation. Regardless of the efforts of their associates in their communities, not in military service, to preserve the work of these men, they realize that on their return to their homes they will have to salvage the greater part of their lost practices. The younger group, called to service before completing their residencies and with only short-term internships, have a common query: How and where can I complete my training? Many of these men, as well as those of the older group, have had to do varying amounts and kinds of war surgery, realize their lack of training and are anxious to get a more adequate experience in civilian surgery. A recent analysis of a pilot questionnaire sent to surgical officers in the Army shows that 77 per cent of the men graduating from medical schools between the years 1936 and 1942 desire further training as surgical residents.

A recent address by Surgeon General Kirk paid unstinted praise to the surgeons in the war zones and in military hospitals in reducing the mortality in casualties to a record 3.5 per cent, and stated that this was due to the selection of surgeons with adequate resident training and from those qualified by the several qualifying boards. Unfortunately, the accelerated medical curriculum and the limitation of postgraduate training to a nine-month internship and a limited number of men in the 9-9-9 plan — a program followed at the insistence of the Army and Navy for military reasons — have effectively stopped the supply and the training of the very group of surgeons who have been responsible for the high standard of service and accomplishment referred to by the Surgeon General. This is indeed a serious situation if the war continues for more than a year, for poorly educated and inadequately trained surgeons will be sent to do the most difficult kind of traumatic surgery. The goose laying the golden eggs is being killed.

This question of how to provide postwar training in surgery for men returning from military service is being discussed by many national medical and surgical organizations. Questionnaires are being sent to all the medical officers here and abroad by the American Medical Association and the American College of Surgeons. There is danger of too many cooks' spoiling this particular broth. The subject is being discussed in Washington, in and out of Congress, but beyond providing for financial aid to the returning medical officer for periods equal to his time in the service, no concrete ideas have thus far appeared in Washington.

It is obvious that the many veterans' hospitals already built and planned, to provide several hundred thousand beds for returning casualties, must be staffed. How to obtain qualified surgeons for these hospitals is one of the postwar problems that is not a congenial or promising topic in Washington. The Clark bill in Congress, not yet reported out of committee, provides, among other things, that the postwar training of medical officers shall be under the Veterans Bureau. The purpose of this bill is obvious. But how adequate will these veterans' hospitals be for such training? This will depend on their location, their proximity to medical teaching institutions and their relations with them and on the ability and experience and compensation of the surgeons and physicians appointed to the staffs of these hospitals. Unless the selection and appointment of the staffs of these hospitals are of an entirely different character from those of the last war, the postwar training of returning medical officers in veterans' hospitals will be a tragedy.

In the questionnaire referred to only 11 per cent of those replying indicated a desire to remain in governmental service, and a smaller percentage desired to work in veterans' hospitals.

In decelerating the medical-school curricula on the basis of the original four-year plan, which is being proposed beginning in 1945, there will be in the following three years a period of nine months to one year when there are no medical students available for internships. This may be of great help in providing places for medical officers, demobilized on a staggered program, to get further hospital training. But it will require the intelligent, patriotic and far-seeing co-operation of the medical boards and boards of managers of the better hospitals all over this country to rearrange the intern and resident training program to provide positions and opportunities for such training. The normal standards of surgical service have been badly compromised, and the ability of hospitals seemingly to function under war conditions with limited and poorly trained assistants will require a re-education of boards of managers to provide room and opportunity for these medical officers returning and desiring further training.

Undoubtedly most of the hospitals will give first choice and priority to the men who as interns or first-year and second-year residents left these hospitals for military service. But in addition a limited provision should be made in all these hospitals for men of demonstrated ability as medical officers to get further resident experience.

It must be realized that with the complete disorganization of medical centers and hospitals in Europe, the pressure from that and other continents

to obtain surgical training in our well-equipped and adequately staffed hospitals after the war will be far greater than ever before. This will only complicate our own difficulties in providing proper facilities for medical officers seeking further surgical experience.

Out of all this complicated and difficult problem there may develop a clearer and more definite realization on the part of the medical profession and the laity that surgery, as a branch of therapy in the science of medicine, should be limited to those having adequate resident training, responsibility and experience. There is an increasing recognition of the importance of such training, as shown by the insistence of hospital boards that appointments to their surgical staffs be made from surgeons adequately trained and qualified by the boards of the several specialties.

The mortality and morbidity rates of the patients of properly qualified surgeons as compared with those of the casual operator engaged in general practice are so obvious to intelligent boards of management that they are insisting on limiting the surgery in their hospitals to qualified surgeons. The high standards of wound healing, preoperative and postoperative care and follow-up results that one finds in a well-trained surgical resident on a three-to-five-year program in teaching hospitals are so far superior to the oldtime self-made amphitheater and circus-performing surgeon that there is no comparison between them. One of the tragedies of this war is the interruption of the well-established program of resident training in so many of the hospitals of this country. It should be our aim and determination to restore this program as soon as the exigencies of war permit.

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EPIDEMIC TYPHUS FEVER AND OTHER RICKETTSIAL DISEASES OF MILITARY IMPORTANCE*

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THE rickettsial diseases of military importance are epidemic typhus fever, tsutsugamushi fever, trench fever, murine typhus fever and Rocky Mountain spotted fever. Although only a few cases of murine typhus fever have occurred in the military personnel during this war, some of them have occurred under circumstances that raised epidemiologic questions that had to be answered. The Rocky Mountain spotted fever group is at this time of least importance, since there is no large body of troops stationed in the endemic area.

Trench fever has been classified as a rickettsial disease and is louse borne. Organisms of the rickettsial group have been reported as recovered from lice and their feces fed on patients ill of trench fever. These organisms have subsequently infected volunteers. Trench fever disappeared following World War I before it was possible adequately to study the disease. It is again reported in Europe, however, and if future military operations require prolonged trench warfare it may recur there. Owing to the efficiency of the newer methods of louse control it should not produce the damage it caused in the last war.

With the exception of Q fever and trench fever, this group of diseases produces in the serums of patients agglutinins for the X strain of the proteus bacillus — *Proteus vulgaris*. There is no known strain of proteus bacillus that agglutinates with Q-fever serums, and nothing has been reported concerning agglutinins in trench fever. The Weil–Felix reaction — agglutination of the proteus-bacillus group — is used to differentiate typhus fever, Rocky Mountain spotted fever, tsutsugamushi fever and other febrile exanthematous diseases. The serums of patients suffering from spotted fever and typhus fever agglutinate with OX19 and OX2 strains, whereas the serums of patients with tsutsugamushi fever agglutinate the OXK strain.

Epidemic Typhus Fever

The synonyms of epidemic typhus fever are as follows: shipboard fever, jail fever, putrid fever, petechial fever, typhus exanthematicus, *Fleckfieber* (German), *typhus exanthematique* (French), *el tabardillo* (Spanish) and *typho-esantematico* (Italian). It may be defined as an acute infectious disease caused by *Rickettsia prowazeki*. In the majority of cases the onset is abrupt and is accompanied by a fever lasting about fourteen days, usually followed by a critical fall or in some cases by a rapid lysis of temperature. A striking feature of this disease is a "rose-spot" eruption that appears from the fifth to the sixth day of the disease, usually on the abdomen or loins and extending over the trunk and extremities. Under pressure the rash fades, radiating in a stellate form from the middle of the rose-red macule or papule. Other prominent features of the disease are profound stupor

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and deafness, which may continue for months after the patient is well.

Epidemic typhus fever has probably killed more persons during periods of wars and famine than has any other disease. Medical history is indebted to Fracastorius for describing the first epidemic of typhus fever that can be readily recognized as such, as well as subsequent epidemics occurring in Italy from 1505 to 1530. Hirsch wrote of typhus fever as follows:

> The history of typhus is written in those dark pages of the world's story which tell of the grievous visitations of mankind by war, famine and misery of every kind. In every age, as far back as the historical inquirer can follow the disease at all, typhus is met with in association with the saddest misfortunes of the populace; and it is, therefore, a well-grounded surmise that the numerous pestilences of war and famine in ancient times and in the Middle Ages, which are known to us . . . had included typhus fever as a prominent figure among them.

The scientific epidemiology of typhus fever began in the early part of the sixteenth century. It was rife over the greater part of Italy from 1505 to 1530. Soon thereafter numerous epidemics were reported from almost all the European states. The political and social disturbances of the seventeenth and eighteenth centuries and the first thirty years of the nineteenth served to spread repeated epidemics to all parts of Europe.

The epidemiologic records of the eighteenth century reveal that there was scarcely a year in that period in which great or small typhus-fever epidemics did not occur. In brief there are four periods of special importance. The first period began about 1690 and ended about 1720. Austria, Germany and Hungary were particularly involved, and Ireland had three severe epidemics, the two last having spread to England and Scotland. The years 1734–1744 comprise the second period, when Central and Eastern Europe were involved. It was a war pestilence in company with typhoid fever and the dysenteries. It is noteworthy that of all the great wars of which there is record, the American Civil War and the Franco-Prussian War in 1870 are the only ones in which epidemic typhus fever did not have a prominent place. The Seven Years' War and the war between England and Spain ushered in the third period (1757–1775). A severe famine occurred in Europe at that time and produced conditions favorable for the disease to spread. The revolutionary wars in France started the fourth period, which was by far the severest epidemic period of typhus fever in the eighteenth century. This period began about 1790 and lasted until the conclusion of peace in 1815. During that time typhus fever spread all over Europe. It was severest in the war-ravaged countries, but did not spare populations remotely removed from military concentrations or the travel routes of troops.

The Western Hemisphere had its first experience with epidemic typhus fever in Mexico, following the Spanish Conquest, where it became epidemic in 1530. Pizarro began the conquest of Peru in 1526, and typhus fever soon appeared in the highlands of South and Central America, where it remains as an endemic disease known as *tabardillo*. Canada's first experience with the disease appears to have been in 1659, with several recurrences in the eighteenth and nineteenth centuries. The first great wave of Irish immigration to Canada was in 1847, the immigration and quarantine records showing that 84,445 persons immigrated to Canada that year. Of this number 75,540 came from Ireland. Among these, 30,265 persons contracted typhus fever. Of this number, 5293 died during the various voyages at sea, 8012 at Quebec and 7000 at Montreal — a total of 20,305 deaths. Several times during the eighteenth and nineteenth centuries typhus fever appeared in the seaports of the United States. Philadelphia had its last reported epidemic in 1883 and New York in 1893. Flippin in 1938 reported that 27 cases of epidemic typhus fever had occurred in Philadelphia since 1911. For some unaccountable reason louse-borne typhus fever has never established an endemic focus in either Canada or the United States.

The important endemic foci of typhus fever at the present time are China, Russia, Turkey, Syria, Iran, Irak, Arabia, Afghanistan, Spain, parts of France, eastern Europe, Germany, Italy, North Africa, parts of Central Africa and the mountainous sections of Central and South America.

Early in the present war, typhus fever began to increase in certain parts of Europe, North Africa and the Middle East. In 1942 the reported increase became so important that several conferences between representatives of the Army, Navy and United States Public Health Service were called, and in the fall of that year the United States of America Typhus Commission was established by executive order of the President.

The most important epidemiologic features of epidemic typhus fever are as follows: It spreads rapidly among distressed populations disorganized by famine or war. It usually appears first in concentration camps, prisons and slums. It is a disease of cold weather; Hirsch analyzed one hundred and forty-seven epidemics and reported that thirty reached their peak in spring, twenty-eight in winter and spring, eighteen in autumn, seventeen in summer and fourteen in autumn and winter. It is associated with a louse-ridden population, and is readily transmitted from person to person by the body louse. An attack usually confers a long immunity; some investigators believe that the severer is the attack the longer is the immunity.

Epidemic typhus fever is transmitted by the louse *Pediculus humanus*. Nicolle, Conte and Conseil in 1909 proved by experiment that the chimpanzee could be infected with the disease by the injection of a small amount of blood from a human case in the active stage of the disease. They then infected

monkeys and proved that it could be transmitted from monkey to monkey by bites of the infected body louse (*Ped. humanus* var. *corporis*). This work was confirmed in the United States in 1910 by Ricketts and Wilder. From the work of Goldberger and Anderson it seems clear that the head louse (*Ped. humanus* var. *capitis*) may transmit the disease under experimental conditions. It is not, however, regarded as an important vector.

Hume reports that the physicians in Serbia in the last war recognized the louse as the vector but believed that there were other methods of infection, especially favoring the inhalation theory. It was shown in 1923 by Arkwright and Bacot that rickettsias could survive in the feces of infected lice at room temperature for eleven days. The high mortality rate among physicians, nurses and orderlies in typhus-fever epidemics — especially since this group of persons is nearly always surrounded by many precautions against lice — strongly suggests that actual contact with lice is not always necessary. Since rickettsias are known to remain viable and to retain their virulence for at least eleven days in dried feces of lice, since experimental animals have been infected by intranasal inoculation, and since laboratory workers and others have contracted typhus fever in an unexplained manner, it seems highly probable that the inhalation of rickettsias in dried feces of lice has been responsible for some cases.

The most frequently reported period of incubation is eight to twelve days, but the period varies from five to fifteen days. The onset may be accompanied by a chill, usually not severe, which may be preceded by a few days of malaise, nausea, severe headache and loss of appetite. The fever usually reaches its maximum by the end of the first week. Morning remissions of fever are frequently seen, but are usually not very marked in the second week, by the end of which time the temperature usually falls by a rapid lysis, except that in complicated cases the patient does not become afebrile until the sixteenth day.

One of the most difficult symptoms to control is severe headache. Cardiac weakness and profound prostration may be seen from the very onset of the illness, and are usually most prominent in the second week. Constipation is a frequent and troublesome feature. The teeth are covered with sordes, which requires strict nursing care to control. Otitis media and parotitis are connected with this condition. The conjunctivas are injected. All the symptoms, especially the cardiac ones, may become exaggerated on the appearance of the rash. Nosebleed may occur.

Mental disturbance is usually seen by the end of the first week and may vary from confusion, disorientation and restlessness to terrifying hallucinations that sometimes end in the patient's jumping from a window. Some of these symptoms may remain in varying degrees of severity for weeks or months after the acute illness is over. Owing to the circulatory disturbance, gangrene, especially of the toes and less frequently of the fingers, is sometimes seen. It is often bilateral.

In uncomplicated cases with recovery there is a dramatic change in the condition at about the fourteenth day. The temperature falls and the mental condition greatly improves. In older patients the prostration and cardiac weakness may remain for a considerable period of time. As a rule younger patients make a more rapid recovery. Sequelae are rarely seen.

Cough is extremely frequent and may appear from the beginning of the illness, but is usually most annoying on the appearance of the rash. By the beginning of the second week the cough usually becomes less troublesome and various rales may be heard. Death from bronchopneumonia is frequent. Physicians in the Middle East report an unusual number of cases of bronchopneumonia in the present epidemic. Several physicians with extensive experience in this epidemic believe that some degree of bronchopneumonia is always present. They point out that in previous epidemics there was such a shortage of physicians that careful physical examinations were frequently impossible.

The eruption appears usually around the fourth day about the flanks and axillas and spreads to the chest and back. It is usually more pronounced on the back. It is seldom seen on the face, but is seen in the palms and on the soles. The rash lasts a varying time — from a few days to weeks. Occasionally markedly hemorrhagic rashes are accompanied by hematuria, hematemesis and melena which indicate a poor prognosis. The rash at onset easily disappears on pressure, leaving stellate radiations. Later it does not disappear so easily on pressure and becomes petechial.

A prominent feature is cardiac weakness due to myocardial damage. The heart sounds are weak, with a rapid, irregular pulse. The blood pressure is often quite low. Bradycardia is frequently seen in convalescence.

There is no characteristic blood finding. Leukopenia may be present in the first few days, but in uncomplicated cases the white-cell count rises to 10,000 or 15,000.

Albuminuria may be present from the onset, but disappears with convalescence.

Diagnosis

The most important laboratory finding is a positive Weil–Felix reaction during the second week of the disease. It reaches its height during convalescence and may rapidly disappear. For diagnostic purposes a test should be made in all suspected cases and repeated late in the second week. With a good antigen the serums of patients ill of typhus fever frequently reach titers of 1:10,000 to

1:100,000. The OX19 strain of the proteus bacillus is most frequently used, because it is more frequently agglutinated than is OX2. This reaction has no practical value in differentiating Rocky Mountain spotted fever from typhus fever. There are diseases not caused by the rickettsias that may show a titer in dilutions of 1:320 and occasionally higher.

An important recent advance is the utilization of the complement-fixation test in the diagnosis of typhus. In this test rickettsias of epidemic typhus fever are used as an antigen. The test becomes positive in the second week and may remain positive for the life of the patient.

On gross examination little is seen at autopsy except the fading rash, the complicating bronchopneumonia and splenic enlargement. Fraenkel in 1914 described the essential lesion as distinguished by injury to the capillary and precapillary vessels, characterized by proliferative changes in the endothelium of the arterioles and arterial capillaries, followed by necrotic changes, chiefly in the vessels of the skin, myocardium and central nervous system. There is a perivascular infiltration of small round cells. The lesions, which are microscopic in size, are most frequent in the skin, heart, great vessels, adrenal glands, testes, kidneys and brain, with the cerebral cortex usually the most involved part. Quite characteristic are the small paracapillary nodes of microglia. Plasma-cell infiltration and frequent thrombi have been reported. Splenic hemorrhages are frequently seen.

No specific treatment has proved of value. Many of the more recent chemotherapeutic agents have been used, with little success; in several cases there was evidence of harm from them. Convalescent human serums and serums from horses inoculated with rickettsias have been tried, with little benefit. A hyperimmune rabbit serum has been used in a small series of cases, with indications that it is valuable.

For the relief of the headache, acetylsalicylic acid is frequently not enough and resort to codeine or morphine is necessary. Constipation should be controlled, preferably with mild laxatives or enemas. Digitalis is of value in cases showing cardiac failure. Cardiac depressants are to be avoided. Every precaution should be taken to conserve the patient's strength. Good nursing is essential to prevent bedsores. In severe cases, particularly in elderly persons, the patient should be confined to bed until convalescence is well advanced.

This disease can be controlled by the destruction of lice. In a campaign against epidemic typhus fever, measures should be taken to include all persons in infected districts. This can only be done by house-to-house inspection, with removal of patients to hospitals and disinfestation of all contacts, their clothing and houses. A quarantine should be established and all persons coming from typhus-infected areas should be treated as contacts. Clothing and bedding can be disinfested either by heat or by chemical means, that is, by the new louse powders. A recent popular article reports that 1,300,000 persons were deloused in Naples in January of this year and that one application of the powder to the clothing was effective for about six weeks.

The body louse nests in the seams of clothing, and the louse-infested person should be bathed and the hair of the body and head should be clipped. In female patients great resistance to clipping is frequently encountered. Where this resistance is based on social customs or religious beliefs, it is far better to resort to oil and chemicals to kill the lice than to come in conflict with folkways. The new powders effectively solve the problem.

Physicians, nurses and orderlies in hospitals caring for typhus-fever patients should be provided with closely woven white-cotton, louse-proof garments fashioned like coveralls and open at the neck, wrists and ankles. Socks should be pulled over the bottoms and rubber gloves used over the wrists, and the neckband should be tightly closed. Because of the probability that infections have occurred from the inhalation of dried feces of lice, great care should be exercised in examining patients and in handling their bedding and clothing.

Several types of vaccine have been prepared for immunizing against typhus fever. Attenuation of living rickettsias by heat or other means has been employed, but the inherent danger of using vaccines of these rickettsias has been shown by the fact that typhus fever has been produced by some of them. Rickettsias killed by phenol or formaldehyde are also used. The Weigl vaccine is reported to give good immunity, but it cannot be produced in large quantities. It is made by the injection of a suspension of rickettsias into the rectums of lice, which are subsequently fed on typhus fever-immune persons, after which the louse intestines are removed and prepared as a suspension that is used as a vaccine. About 200 lice are required to prepare a vaccine for one person. Vaccines made from killed rickettsias from the lungs of intranasally infected rats, mice or rabbits have been used.

The vaccine in use by the United States armed forces is the modified Cox vaccine, which is made from killed rickettsias from the developing yolk sac of the chick embryo. This vaccine gives good results in laboratory animals, but lacks adequate field tests in human beings. Typhus fever has occurred in a number of laboratory workers and in about 50 members of the armed forces, all of whom have been vaccinated, but there have been no deaths. It is the consensus that this vaccine has greatly modified the course of the disease in those who have acquired typhus fever subsequent to vaccination. It is used in a series of three inocu-

lations, with a booster dose every few months when in a typhus-fever area.

Endemic Typhus Fever

The synonyms of endemic typhus fever are: murine typhus fever, Brill's disease and Mexican typhus fever (*Tabardillo*). The causative agent has been named *R. mooseri*. Brill in 1898 described a form of febrile disease of unknown origin that resembled typhoid fever but gave a negative Widal reaction. He noted that epidemiology of the disease differed from epidemic typhus fever in that it occurred sporadically in a louse-free population and was milder in character than the latter and had a different seasonal occurrence. These facts caused him to suspect some other vector than the louse as responsible.

Maxey's work in the southern United States disclosed that most of the cases occurred among food handlers. This caused him to conclude that the reservoir in nature is the common rat. It seems likely that other rodents are also responsible.

Zinsser studied the records of 538 cases of Brill's disease that occurred in Boston and New York City between 1910 and 1933. Of these, about 95 per cent occurred in foreign-born persons who had migrated from Russia. Ninety-seven per cent of all the cases from 1910 to 1920 were in Jews, and over 80 per cent of the patients came from Russia. Zinsser believed that the cases of Brill's disease represented recrudescences of infections acquired in Europe.

Endemic typhus fever has occurred in all the southeastern states and as far north on the East Coast as Boston, in the coastal cities on the West Coast and in Texas. In 1929 the human cases were largely limited to towns and cities. Nashville, Tennessee, had about 75 cases in 1941. There are additional foci in Cincinnati and Cleveland, Ohio.

Since endemic typhus fever became well known in the United States it has been found in many parts of the world, especially in coastal cities. It is known to exist in Australia, the Philippines, China, Indo-China, Manchukuo, Malaya, Syria, Lebanon, Palestine, Egypt, Greece and southern Europe. In Africa it was believed that many cases of endemic typhus fever were diagnosed as epidemic; however, all the strains isolated by the United States of America Typhus Commission are of the endemic type.

The epidemiologic aspects of the disease are as follows. The peak of prevalence is in the late summer and fall. In the United States the disease has occurred most frequently among workers in food-handling establishments. The literature records that human cases are associated with rat harborages. (I saw 6 cases in Australia in September, 1943, in which connection with rats, mice or fleas seemed highly improbable.) The disease is not confined to slums. Transmission from person to person by contact with rat fleas has not been proved.

Except for the milder course of the disease the clinical features are identical with those of epidemic typhus fever. The rash does not usually appear before the fifth day, and except in severe cases is not so extensive as in epidemic typhus fever. In mild cases only a few macules appear, and they may disappear in a few days. The general symptoms are milder.

The mortality rate in the United States is below 5 per cent, and most of the deaths occur in persons over forty-five years of age. In the Middle East, physicians believe that a careful compilation of statistics would reveal a higher fatality rate. This may be explained by the present food conditions. The general food supply is well below that of normal times, whereas in the United States the experience with murine typhus fever has been confined to a population not under stress of war and not living on such restricted subsistence levels.

This disease has frequently been confused with drug rashes, typhoid fever and meningococcemia. A diagnosis cannot be made until the rash appears. In localities where epidemic typhus fever, Rocky Mountain spotted fever and tsutsugamushi disease occur the diagnosis must be established by laboratory methods. The Weil–Felix reaction is positive in high titers.

In the light of the present knowledge the control of endemic typhus fever rests on the control of the rat population. The case against the rat is sufficiently strong, because of other diseases and economic considerations, to cause the medical profession to increase the fight against it. It has been estimated that the rat population in the United States is in excess of 250,000,000. In the opinion of competent mammalologists this estimate is too low. They believe that each rat consumes $2 worth of food and damages $20 worth of food a year. This economic waste runs into billions of dollars and is entirely unjustified in peacetime; in wartime with world-wide food rationing it is intolerable. Bubonic plague has recurred in Palestine, and if it should be introduced into one of our eastern seaports it would be necessary to destroy rats on board ships sailing from a foul to a clean port. This would seriously interfere with wartime shipping.

It is extremely interesting to note that medical men have been slow to employ trained mammalologists in the fight against rats, yet they have extensively employed entomologists in the control of disease-bearing mosquitoes.

Vaccines have been prepared from the rickettsias of endemic typhus by the same technics as for epidemic typhus fever. They show good protection

in laboratory animals, but there is no adequate experience with them in human populations.

Tsutsugamushi Fever

The synonyms for tsutsugamushi disease are kedani mite disease, Japanese river fever and mite (scrub) typhus fever. Until the advent of World War II the American literature has been singularly lacking in reference to this disease.

Japanese physicians claim that the disease has been recorded for more than a thousand years. The first clinical report was published by Palm in 1878. Hayashi first named the organism causing this disease in Japan, *R. tsutsugamushi*. Kawamura and Imagawa worked with the organism and identified it as *R. akamushi*. This work was confirmed by Ogata who retained the original name *R. tsutsugamushi*. There is excellent reason to believe that these organisms are identical. Lewthwaite and Savoor did exhaustive cross-immunity tests and showed the similarity between scrub typhus fever and tsutsugamushi disease by both intraocular and intradermal reactions in rabbits and monkeys. From cross-protection tests between the rickettsias of Samatran fever and the tsutsugamushi disease of British Malaya performed on monkeys and rabbits it appears that these diseases are identical. In addition to these reasons, it should be borne in mind that travel in those parts of the world is sufficiently great so that persons could easily be transported to those areas well within the period of communicability of this disease and infect the vector and animal reservoir.

In Japan the larval form of the harvest mite locally known as the kedani mite (*Trombicula akamushi*) is the vector of this disease. There are several species and variants within species of trombicula, and they may be vectors in different localities. Little is known of the habits of the trombicula. The larvae are microscopic six-legged creatures that move along the ground or cling to the vegetation until they attach themselves to a passing man, bird or animal. The eggs are laid 8 to 10 cm. under the surface of the ground and when hatched pass through several stages to the adult form. Animal and bird life is abundant in Australia and the islands of the Southwest Pacific and provides the necessary blood meal for these larval mites. The evidence is that the larval mite is infected from the parent and passes the rickettsia on to man. Much work is needed before a final answer can be given on the relation between the several variants of trombicula. At least three species are under suspicion by the Australian and United States Army medical officers. The trombicula larvae attack man on all parts of the body, but the most frequent sites are the scrotum, groin and armpits. Numerous ticks are found in Australia and the islands of the Pacific and until proved innocent should be regarded as additional vectors.

Rats are abundant in the islands of the Pacific, and it appears likely that the local rat is the principal reservoir. Gunther, however, has listed some seventeen hosts for the larval mite. These include such birds as the bush fowl, swamp hen and parrot. It seems probable that migratory wild fowl are likewise hosts and spread the mites from one island to another. Lizards are frequent in these islands and also have been known to be infested with mites.

Ahlm and Lipshutz have recently reported on a series of 70 cases of tsutsugamushi fever in the Southwest Pacific. The most frequent location of the primary lesion was the scrotal area, although the inguinal and ankle areas were frequently involved. The incubation period was seven to fourteen days. The patients complained of frontal headache, generalized aches and pains, backache, weakness, insomnia, chilliness and fever that rose slowly to a peak of 104 to 105°F. within ten days. The pulse was slow in proportion to the temperature rise. The temperature fell by lysis. A small number of patients complained of pain in the abdomen, with nausea and vomiting and occasional diarrhea. The ulcer varied in diameter from a few millimeters to 1 cm. It was characterized by a central black necrotic area and was surrounded by an indurated, red areola. In some cases a lymphangitis was observed. The lymph nodes were the size of a walnut and smooth and tender and were not attached to adjacent nodes. They did not suppurate. The adenitis appeared from three to four days after the onset of symptoms. Conjunctivitis with mild edema of the eyelids was present. Weakness and general myatonia were pronounced. A pale, raspberry-colored erythematous rash, patchy in nature, was observed on the face, chest and abdomen and appeared about the fourth day. Sixty-seven per cent of the patients showed signs of severe atypical pneumonia, with a dry cough, scanty expectoration, dyspnea and tightness over the sternum. In a few cases there was evidence of consolidation. X-ray examination of 20 per cent of the cases showed atypical virus-like pneumonia. Epistaxis was seen in 20 per cent of the cases. Conjunctival hemorrhage occurred. Abdominal distention with nausea and vomiting was found in 60 per cent, and auditory disturbance in 34 per cent, with marked diminution of hearing to almost complete deafness. Hallucinations, disorientation, insomnia and nervousness were outstanding features. The fever continued for ten to fourteen days, during which time the patients were extremely weak and perspired profusely. Myocardial damage was observed late in the disease. In 3 per cent of the cases it was manifested by gallop rhythm, reduplication of the mitral first sound and muffled apical sounds, which were regarded as poor prognostic signs, and it was present in the one death that occurred. The specific agglutination test against the OXK strain of proteus bacillus became

positive about the end of the second week. A few cases never became positive. Convalescence was prolonged.

The American literature contains no reports of distinctive gross lesions. Lewthwaite in his study of rural tropical typhus fever in the Malay Peninsula found petechial hemorrhages in the heart, lungs, alimentary tract and kidneys. The brain showed perivascular infiltrations more especially frequent in the pons and medulla and also occurring in the cerebellum. Thrombus formation was noted in some of the capillaries.

In the endemic area the diagnosis should not be difficult, since the history and initial lesion are quite helpful. The presence of OXK and the absence of OX2 and OX19 agglutinins should clear the diagnosis.

It is generally agreed that the most important factor in the treatment of tsutsugamushi disease is absolute bed rest and symptomatic treatment. There is a difference of opinion about the adequacy of acetylsalicylic acid in the control of headache. Ahlm and Lipshutz discontinued the use of codeine because of abdominal distention, which interfered with fluid intake. Several Australian medical officers found acetylsalicylic acid inadequate. Generally the patients with pneumonic signs were given one of the sulfonamide drugs in adequate doses, with no appreciable results. All agree that there is a vitamin deficiency. The use of digitalis was disappointing, as was the use of oxygen. The use of sedatives in adequate doses cannot be overrated.

Convalescent serum was considered, but was not used because there is no exact knowledge when the blood is free of rickettsias and because of possible shock following its use.

The wearing of mite-proof clothing has been recommended by the Japanese and others, but anyone who has attempted to work in the endemic areas of the tropics will realize that this measure is impractical. Excellent results from the use of insect repellents have been reported by the Australian medical authorities. Camp sites should be carefully selected and if possible be prepared by natives. The grass should be cut to destroy the habitat of possible vertebrate reservoirs and mites. Rigid control of rats is necessary. Men should be provided with hammocks and should not sleep on the ground. Spraying the ground with a petroleum emulsion of one of the new insecticides should be considered. The value of any repellent is in its proper use. Those exposed in an endemic area should be carefully instructed in the use of repellents and especially told to dust their socks and trousers carefully. If the clothing is thoroughly treated with insecticide there is no reason to expect a mite to pass through its meshes.

Trench Fever

During World War I trench fever was known as five-day or Wolhynia fever. This disease disappeared after the war and its true relation with the rest of the rickettsial diseases is unknown. It is louse borne and extracellular rickettsias have been found in lice fed on patients ill with this disease. Rickettsias are found in the feces of lice fed as indicated. There is no report of agglutination of X strains of proteus bacillus by patients' serums. The incubation period is from five to twenty days. The onset is sudden, with a quick rise of temperature, which may last from a few days to over a week. A number of relapses is the rule, which makes this an important contributor to lost days. There is no specific treatment. Prevention is by control of lice.

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THE DIFFERENTIAL DIAGNOSIS OF WEAKNESS AND FATIGUE*

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ONE of the problems most frequently encountered by the general practitioner and the internist is a complaint variously described as weakness, exhaustion, fatigue, loss of ambition, low vitality or weak spells. Weakness and fatigue, alone or dominating a group of other symptoms, cause thousands of people to suffer disability and a greatly lessened enjoyment of life. What can the physician do to investigate these complaints and how can he determine their cause? To present an answer to this question from our experience at the Lahey Clinic, data have been compiled on 300 consecutive cases in which weakness, fatigue or weak spells were the chief complaint.

RESULTS

In 61 cases (20 per cent), the complaint was caused by a physical disorder (Fig. 1). In 239 cases (80 per cent), it was apparently not due to a physical disorder but was the result of a nervous state of one kind or another. Weakness due to hunger and fatigue caused by hard labor were not encountered. However widespread these conditions may be, they are not likely to bring the patient for medical attention.

Of the 61 cases in which a physical disorder was found to be the cause of weakness, it was possible in 28 cases to make the diagnosis by clinical observation alone, the history and physical findings pointing to the cause and nature of the disorder. In 20 cases, the disease was hidden and the diagnosis could not be made without laboratory tests or roentgenograms. Thirteen cases were on the borderline, and special laboratory work or roentgenograms were needed to confirm or disclose the diagnosis.

An analysis of the physical disorders causing weakness and fatigue represented by this series is shown in Figure 2. Chronic infections, including tuberculosis, and even more frequently nontuberculous pulmonary infection, sometimes in the convalescent period, were found in 13 of the 300 cases (4 per cent). Metabolic disorders were found in 12 cases (4 per cent)—8 of diabetes and 4 of myxedema. In 8 cases (3 per cent) there was heart disease. In 16 cases (5 per cent) there were neurologic disorders including 4 cases of myasthenia gravis, 8 of narcolepsy and 3 classified as psychomotor epilepsy. Anemia of different types was found in 5 cases. Miscellaneous causes accounted for the remaining 4 cases, including 1 each of carcinoma of the lung, vitamin deficiency, recurrent fever possibly due to Hodgkin's disease and unclassified low-grade fever.

It should be noted that complex problems and unusual conditions are more likely to be seen in hospital or clinic work than in general medical practice. Furthermore, a relatively small series such as this one can give only the general trend of distribution of cases. A larger one would almost certainly include important disorders that were not present in this group, such as Addison's disease and subacute bacterial endocarditis. Yet these observations give a fair picture of what the physician may expect to encounter when consulted by a patient who complains of weakness.

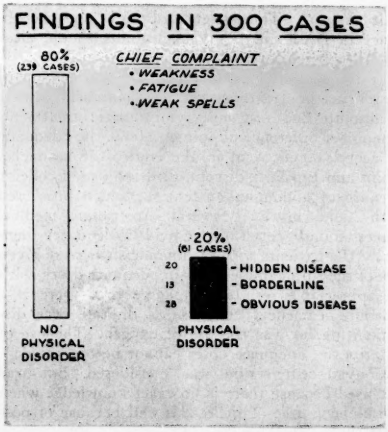

FIGURE 1.

CURRENT LAY OPINION

If these causal conditions are compared with those usually blamed for weakness and fatigue, a considerable deviation from current lay and medical opinion is noted (Table 1). In the minds of the public, lack of energy tends today to mean lack of vitamins. This idea has been exploited by the manufacturers of vitamin products. Our experience lends no support to the theory that vitamin deficiency seriously affects the health of a large percentage of the population. In this representative group of 300 cases there was only 1 in which vitamin deficiency was held responsible for weakness.

The concept of vitamin deficiency as a cause of lack of energy has now surpassed the still widely

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held theory that *constipation* is responsible. This ancient idea has been kept alive in modern times by equally vigorous advertising. There was no case in this series in which weakness or fatigue could be blamed on constipation. Although it may be true that some people have an increased sense of well-being with daily evacuation of the bowels, ill effects from so-called "poor elimination" have been tremendously exaggerated.

A *sluggish liver* has frequently been blamed for lack of energy, a charge of which this important organ of the body is almost innocent. Even when hepatic disease has led to a breakdown in liver function, symptoms other than general weakness or lack of energy are likely to appear. Yet it has been observed that patients who have had jaundice may continue to feel weak for many months afterward.

General weakness is generally blamed on a *weak heart*, but all cardiologists agree that this is not a frequent symptom of heart disease. In this series it occurred in only 8 cases (3 per cent). In the majority of cases, heart disease brings about other symptoms that cause the patient much more concern, such as dyspnea, pain in the chest and swelling of the feet. It should be pointed out that when a patient with a heart lesion complains only of weakness, this symptom is not likely to have any relation to the heart. In cases of neurocirculatory asthenia the patient may complain of weakness, but the chief complaint is oftener palpitation or dyspnea.

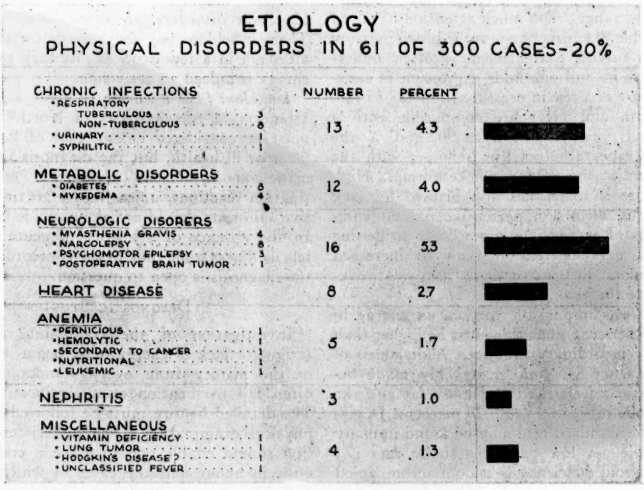

FIGURE 2.

Cancer is frequently feared when chronic ill health of any kind appears, but it was found in only 2 cases (0.7 per cent). Cancer seldom causes weakness and exhaustion unless it is so far advanced that anemia or cachexia has resulted. Carcinoma of the cecum or ascending colon may lead to advanced anemia before other symptoms have attracted attention, but as a rule other symptoms precede and supersede in importance the complaint of weakness. With Hodgkin's disease, chronic ill health with lack of energy is often the dominant complaint.

TABLE 1. *Conditions Considered Frequent as a Cause of Weakness but Rarely Encountered.*

CONDITION	ACTUAL INCIDENCE	
	NO. OF CASES	PERCENTAGE
Lay opinion:		
Lack of vitamins	1	0.3
Poor elimination	0	0
Sluggish liver	0	0
Weak heart	8	2.7
Cancer	2	0.7
Medical opinion:		
Anemia	5	1.7
Blood pressure	0	0
Thyroid disease	4	1.3
Adrenal deficiency	0	0
Pluriglandular disorders	0	0
Undulant fever	0	0

CURRENT MEDICAL OPINION

A comparison of these actual observations with current medical opinion regarding the causes of weakness and fatigue also shows important differences.

One finds *anemia* high on the list of conditions often treated for the complaint of weakness. It was found in only 5 cases (1.7 per cent). Attention is sometimes wrongly focused on minor deviations from the normal in the hemoglobin and red-cell count. Furthermore, the frequently used Tallqvist test for hemoglobin may give fallacious readings. In general, one may safely say that anemia does not cause weakness unless the hemoglobin drops below 70 per cent and the red-cell count well below 4,000,000.

A diagnosis of *low blood pressure* is often made when the blood-pressure readings are actually within normal range. Too much attention has been paid to possible ill effects of a systolic blood pressure below 110. Intensive treatment is often undertaken to raise it, and one finds expression of satisfaction because of a rise in pressure from 105 to 115. Perfect health and vigor are compatible with a systolic blood pressure as low as 90, and on the average the expectation of life is longer with the blood pressure at the lower range of normal. High blood pressure is sometimes also blamed for lack of energy, but when a hypertensive patient complains of lack of energy it is more likely to be due to increased nervous tension than to increased vascular tension. In none of these cases was weakness related to the blood pressure.

Myxedema was responsible for lack of energy in 4 patients (1 per cent), but this must be higher than the incidence in ordinary practice. A diagnosis of thyroid deficiency is often mistakenly made because the patient feels tired and looks fat and the basal metabolic rate is −15 or −20 per cent. Deviations from the standard rate may be found in many healthy people. A low basal metabolic rate not related to thyroid deficiency is seldom accompanied by any change in health, but there are a few patients who have diminished energy. The diagnosis of thyroid disease should not be made unless a low metabolic rate is accompanied by clinical evidence of the condition. If there is any doubt, a determination of the blood cholesterol level may aid the diagnosis more conclusively than does the basal metabolic rate. The blood cholesterol is almost invariably above normal in the presence of hypothyroidism; if one finds a low metabolism without high blood cholesterol, thyroid disease can usually be excluded.

Hyperthyroidism causes weakness, but it is seldom the chief complaint except in the severe long-standing cases and in the apathetic cases of old age.

Addison's disease is manifested by the most extreme weakness, but it is a rare disease. In far-advanced cases, the diagnosis readily is made from the clinical picture, including abnormal pigmentation, hypotension, gastrointestinal disturbances and loss of weight, in addition to the asthenia. In early or borderline cases the diagnosis may be aided by special tests. One of these, introduced by Kepler and his co-workers,* is simple and easy to perform. The patient restricts his fluid intake and saves all the urine passed during the night for a period of nine hours. The following morning he is given four to six glasses of water (9 cc. per pound of body weight), and the excretion of urine is measured each hour for four hours. If the excretion in any one hour exceeds the total volume of urine excreted during the night, Addison's disease can be excluded. If there is a low excretion, Addison's disease may be present, but to rule out other conditions that may interfere with water balance, further study is needed.

Other *endocrine conditions*, especially pluriglandular disorders, are often blamed for fatigue. There is seldom any sound basis for the diagnosis, although in a few cases of pituitary tumor lack of energy is indeed an early sign.

Undulant fever is currently given a great deal of attention in certain parts of North America. It must be considered in any case of long-continued fever or ill health, but the diagnosis should not be made on insufficient evidence. Positive agglutination reactions, unless in a high titer, and positive skin tests should not alone decide the diagnosis. In the absence of a history of acute or subacute febrile illness some time in the course of the disorder, the diagnosis is open to question.

Diagnostic Studies

Investigation of the complaint of weakness, fatigue or lack of energy must begin with a review of the history from every standpoint. Patients often fail to mention even significant symptoms. The detailed history must be followed by a careful physical examination. The history and examination should enable one to make a complete diagnosis in about half the cases in which a physical disorder is responsible for the complaint. It should also enable one to suspect hidden or practically hidden disease and should furnish clues to the complete diagnosis.

It is often assumed that the diagnosis of a nervous state must be deferred until the examination, laboratory tests and roentgenograms have ruled out a physical cause for the complaint. This is the wrong point of view. The diagnosis of a nervous state should be made by direct observation of the characteristics of such condition and not be reached entirely by exclusion. If the patient has a physical disorder and a nervous state, they must both be recognized and evaluated in order to make a complete diagnosis and to undertake effective treatment.

Characteristics of Nervous States

One must suspect that weakness and fatigue are due to a nervous state under the following circumstances: when the lack of energy is greatest in the

*Robinson, F. J., Power, M. H., and Kepler, E. J. Two new procedures to assist in recognition and exclusion of Addison's disease. *Proc. Staff Meet., Mayo Clin.* **16**:577-583, 1941.

morning and decreases during the day; when days with excellent vigor are followed by days of exhaustion, with no change in activity to account for such a difference; when immediate benefit follows the use of a medication that has a slow pharmacologic action such as vitamins, thyroid, iron, liver extract and digitalis; when the weakness immediately returns on the omission of the customary treatment with these drugs for a single day; when the patient never has felt really well; when he has been tired and weak for over three years without evidence of a physical disorder; when he complains of nervousness, anxiety and worry and has symptoms that are obviously of nervous origin, such as a lump in the throat, tension in the back of the neck, difficulty in getting a satisfying breath or palpitation; when he denies a nervous state but reveals it by a multiplicity of complaints, variation in emphasis on different symptoms, vagueness of description and nervous behavior, such as flushing and weeping. One must give some attention also to a family history of nervous breakdowns and to a personal history of excessive nervous strain, but these should not be given so much weight as the other factors mentioned.

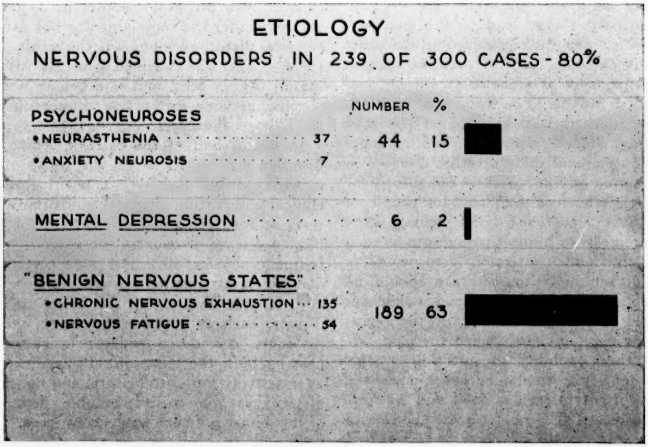

FIGURE 3.

CLASSIFICATION OF NERVOUS STATES

There is need for discrimination in dealing with the nervous states responsible for weakness and fatigue. One should certainly not assume that any nervous condition represents a neurosis. Only one fifth of the patients with nervous disorders were frankly neurotic. The remainder were suffering from benign forms of nervousness that were classified as chronic nervous exhaustion when extreme and simply as nervous fatigue when of milder degree (Fig. 3). The percentage of neurotic patients must be higher than actually exists in the general run of people who have these complaints, because such patients are much more likely than others to seek medical advice. It is important to distinguish the true neurosis from what may be called "benign nervousness," because the treatment must be planned differently (Table 2). A neurosis is largely dependent on intrinsic factors, whereas a benign nervous state is largely dependent on extrinsic factors. The patient with the latter is born with a constitution no different from the average, but he comes to suffer from nervous fatigue or exhaustion because of special stress and strain, overwork, excessive worry or loss of sleep. If he is assured that the physical examination has shown no disorder, he expresses satisfaction. The reaction of the neurotic patient, on the other hand, is one of disappointment. He stresses the serious-

TABLE 2. *Differential Diagnosis of Neurosis and "Benign Nervousness."*

DATUM	NEUROSIS	BENIGN NERVOUSNESS
Etiology	Largely intrinsic	Largely extrinsic
Background	Constitutional inadequacy	Average
Family history	Nervous breakdown (frequent)	Average
Multiple complaints	Usual	Unusual
History	Changeable	Consistent
Onset	Vague	Fairly definite
Duration	Often since childhood	Limited
Reaction to reassurance	Disappointment	Satisfaction

ness of his complaints and insists that some abnormality must be found to account for them.

Diagnostic Procedures to Identify Physical Disorders

To make a complete search for physical disorders, various methods of investigation may be undertaken. These should include in all cases urinalysis and the usual blood tests, such as the red-cell and white-cell counts, examination of the blood smear, determination of the hemoglobin and the Hinton, Wassermann or other test for syphilis. The routine urinalysis may lead to the discovery of diabetes, which can be recognized in no other way. In about half the cases of diabetes seen at the Lahey Clinic, typical diabetic symptoms and complications are absent. The urinalysis may also reveal nephritis and pyelitis. The blood test may disclose primary blood disorders and changes secondary to systemic infection or other disease.

A roentgenogram of the chest is obligatory for all young people who feel tired and for people of any age who have a past history of pleurisy, contact with tuberculosis or respiratory symptoms such as cough. If any hidden infection is suspected, a daily record of the body temperature should be kept for three days or more. The blood-sedimentation rate should be determined, and also the agglutination test for undulant fever when the past history suggests the possibility of infection of this type. Blood-sugar tests should be made when the relation of symptoms to lack of food and to exertion arouses suspicion of hypoglycemia. The basal metabolic rate and the blood cholesterol test aid in the diagnosis of weakness due to thyroid disease, the adrenal-function test of Kepler and his co-workers in cases of suspected Addison's disease, and roentgenograms of the head in detecting enlargement of the sella in cases of tumor of the pituitary gland.

Laboratory tests for vitamin deficiency have not received widespread clinical application. As a rule, a therapeutic test is the best support now available for the clinical diagnosis of hypovitaminosis, although far too often the results are not subject to a control test.

In the neurologic field the prostigmine and quinine tests for myasthenia gravis and the electroencephalogram are available.

Conclusions

In a series of 300 cases in which medical examination was requested because of weakness, fatigue and weak spells, the complaint was found to be caused by a physical disorder in 20 per cent. In the remainder the complaint was not caused by any physical disturbance but was the result of a nervous state. This was classified as a neurosis in approximately 20 per cent, and as a benign nervous state, chronic nervous exhaustion or nervous fatigue in the rest of the cases.

In nearly half of the cases in which a physical disorder was found to be the cause of weakness, it was possible to make a positive diagnosis by clinical observation alone. In the others, laboratory tests or roentgenograms were essential to reveal a hidden disease or confirm the diagnosis. The most frequent physical disorders were chronic infection, diabetes, heart disease, various neurologic disorders and serious diseases of the blood. Certain conditions, such as vitamin deficiency and glandular disorders, considered widespread causes of weakness by both the laity and the medical profession, were actually found to be rare, and not a single case of weakness due to liver trouble, poor elimination or low blood pressure was encountered.

The study of weakness and fatigue leads to a consideration of medical problems covering almost every field of medicine. Although a high percentage of patients with these complaints have no physical disorder, there is a group in which physical conditions of unusual interest may be discovered. In any case these symptoms warrant thorough and complete investigation.

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EXTRARENAL TUBERCULOUS LESIONS ASSOCIATED WITH RENAL TUBERCULOSIS

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RENAL tuberculosis is too often symptomatically silent during the time when it can be treated most successfully. Although the diagnosis of this condition can be made most satisfactorily by the identification of the organism in the urine and can be confirmed by inoculation of laboratory animals, in many cases the disease escapes recognition in its early stages simply because tuberculous infection is not suspected. Hence any symptom, sign or roentgenographic or laboratory finding that may cause one to suspect the diagnosis of renal tuberculosis is worthy of investigation or evaluation.

CALCIFIED MESENTERIC LYMPH NODES

Calcified mesenteric lymph nodes are seen frequently in the routine roentgenograms of the urinary tract. They usually attract attention only when they are so situated as to make it necessary for them to be distinguished from urinary calculi. This is only rarely essential. Although there are several conditions believed to be responsible for the pathologic change in the lymph nodes that is followed by calcification, the vast majority of calcified mesenteric lymph nodes have been the seat of tuberculous infection. This fact prompted us to study the incidence of calcified mesenteric lymph nodes in cases of proved renal tuberculosis. To accomplish this, we carefully examined the intravenous urograms and retrograde pyelograms in 145 consecutive cases of proved renal tuberculosis, in each of which nephrectomy had been performed, so that hence a pathological as well as a bacteriologic diagnosis had been made. This series was compared with a series of 145 consecutive cases of surgically treated renal lithiasis in many of which nephrectomy was performed and in each of which the diagnosis of renal tuberculosis was excluded.

TABLE 1. *Incidence of Calcified Mesenteric Lymph Nodes in Cases of Renal Tuberculosis and of Nontuberculous Renal Lithiasis.*

PATIENTS	RENAL TUBERCULOSIS		NONTUBERCULOUS KIDNEYS	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Men:	81		93	
With calcified mesenteric lymph nodes	8	10	3	3
Women:	64		52	
With calcified mesenteric lymph nodes	11	17	5	10
Totals	19 145		8 145	
Percentages		13		6

Table 1 shows the incidence of calcified mesenteric lymph nodes in both series of cases. Calcified mesenteric lymph nodes were found to be present in 13 per cent of the roentgenograms of patients suffering from proved renal tuberculosis. This incidence was more than twice that found in a comparable series of patients not suffering from renal tuberculosis.

TUBERCULOUS EPIDIDYMITIS

Although it is generally known that renal tuberculosis is fairly frequently accompanied by genital tuberculosis, too often intractable epididymitis is treated for long periods before the kidneys are investigated.

In 34 (42 per cent) of the 81 male cases of proved renal tuberculosis incorporated in the preceding study, genital tuberculosis also was present (Table 2). None of the 93 male subjects in the control group suffered from inflammation of the genitalia.

TABLE 2. *Incidence of Tuberculous Epididymitis and Prostatitis in Cases of Renal Tuberculosis and of Nontuberculous Renal Lithiasis.*

GENITAL INVOLVEMENT	RENAL TUBERCULOSIS		NONTUBERCULOUS KIDNEYS	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Tuberculous epididymitis	31	38	0	0
Tuberculous prostatitis	3	4	0	0
None	47	58	93	100
Totals	81		93	

Thirty-one of the 34 patients had proved tuberculous epididymitis, and the remaining 3 were believed to have tuberculous prostatitis. In 15 of these cases it was necessary to remove the kidney on the same side as the involved epididymis, and in 7 cases the kidney on the opposite side from the involved epididymis was removed. In 9 cases both epididymides were involved.

The frequency of concomitant genital and renal tuberculosis is so great that the genitalia of every male patient complaining of urinary symptoms should be carefully examined for evidence of tuberculosis. Although renal tuberculosis frequently occurs in the absence of genital tuberculosis, the latter is accompanied more often than not by renal tuberculosis. Every male patient who has epididymitis of possibly tuberculous nature should therefore receive complete urologic investigation, even in the absence of urinary symptoms. In this manner the early renal lesions of tuberculosis may be detected.

PULMONARY TUBERCULOSIS

Since we share the general opinion that renal tuberculosis largely if not entirely represents a

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secondary hematogenous focus of tuberculous activity resulting from a primary pulmonary infection, we decided to investigate the incidence of pulmonary involvement in these 290 cases. To do this we reviewed the pulmonary roentgenograms of the 145 proved renal tuberculous patients and the 145 control patients suffering from operative renal lithiasis. As shown in Table 3, each case was relegated to one of three categories: first, the healed or active adult type of tuberculosis; second, the healed childhood type of tuberculous infection, which often is referred to as the Ghon complex; and finally, those cases not showing any pulmonary pathologic change whatsoever, which were designated as negative.

TABLE 3. *Incidence of Pulmonary Tuberculosis in Cases of Renal Tuberculosis and of Nontuberculous Renal Lithiasis.*

Thoracic Involvement	Renal Tuberculosis		Nontuberculous Kidneys	
	No. of cases	Percentage	No. of cases	Percentage
Healed or active adult type	50	34	6	4
Healed childhood type (Ghon complex)	20	14	20	14
None	75	52	119	82
Totals	145		145	

The findings clearly demonstrate the frequency with which renal tuberculosis is associated with healed or active adult-type pulmonary tuberculosis. It is of incidental interest that the frequency of the healed childhood type of tuberculosis was the same in the two series.

Summary and Conclusions

The diagnosis of renal tuberculosis can be established relatively easily once this disease is suspected. Too frequently this condition, whose successful treatment depends on its early diagnosis, is not considered. The incidences of three easily demonstrable tuberculous lesions that are associated with renal tuberculosis have been determined. The presence of either of these associated conditions should cause one at least to suspect renal tuberculosis.

Since roentgenographically evident calcified mesenteric lymph nodes are more than twice as frequent in cases of proved renal tuberculosis as in a control nontuberculous group of patients, the presence of calcified mesenteric lymph nodes in the roentgenogram of a patient suffering from a urologic disease should cause one to consider the diagnosis of renal tuberculosis.

Since epididymitis occurred in 38 per cent of 81 cases of renal tuberculosis but did not occur in a control group of 93 cases, every case of intractable epididymitis should be considered tuberculous until proved otherwise. The condition of the kidneys of such a patient should be promptly evaluated.

Since roentgenographic evidence of healed or active adult type of pulmonary tuberculosis is more than eight times as frequent in cases of renal tuberculosis as in a comparable control group, in every case of renal tuberculosis the patient should have the benefit of a stereoroentgenogram of the thorax. Furthermore, renal tuberculosis should be excluded in any case of pulmonary tuberculosis in which there are subjective or objective urinary findings.

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MEDICAL PROGRESS

MODERN CONCEPTS OF RENAL STRUCTURE AND FUNCTION IN CHRONIC BRIGHT'S DISEASE*

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DURING recent years an intensive application of well-established methods of micromorphology has broadened considerably the knowledge of the anatomic patterns of renal disease. Likewise, great strides have been made toward an understanding of renal pathologic physiology through the development of new functional tests. These two avenues of approach have converged on the central problem of the relation between renal structure and function, and when integrated, allow insight into some of the more remote physiologic disorders and clinical manifestations of renal disease. It is the purpose of this review to discuss recent advances in the pathology and physiology of the kidneys as affected by the various forms of Bright's disease.

STRUCTURE

Factors capable of deforming the architecture of the kidney include vascular disturbances, interstitial tissue proliferation and nephron damage. The last may be secondary to the direct action of noxious agents, to ischemia, to blockage by casts and to the mechanical effects of scar tissue. These factors operate to some extent in all forms of chronic renal disease at a tempo depending on the nature of the primary process, so that each type of disorder is characterized by a distinctive pathology of structure and function, at least early in the course of the disease. In the terminal stages, however, there is a tendency to develop a final common pattern, probably because the same fundamental processes are active in all. Clinically, also, the terminal picture in all forms of Bright's disease is similar.

Vasculature

Vascular changes play a prominent role in the disorganization of renal anatomy. Vascular rearrangement of itself necessarily causes architectural disorder with resulting disturbances in blood supply that directly affect the parenchyma. In all forms of chronic renal disease, the vascular pathology appears to be fundamentally similar but the extent to which it dominates the picture depends on the etiology. In the kidney of essential hypertension it is of prime importance; in glomerulonephritis it is of considerably less importance; and in certain nephroses it is, at first, apparently of little or no importance. In all, however, with time and progression, vascular alterations occur and probably contribute to further damage.

The unique circulatory pattern of the kidney is such that interference with the flow of blood through the glomerulus would be expected to disturb the flow through the peritubular capillaries and cause damage to the attached tubule. This surmise has been supported by the finding that direct communications between the interlobular or arcuate arteries and the peritubular capillaries are absent, or at least exceptional, in the normal kidney.[1] Thus it has seemed reasonable to explain tubular damage in glomerulonephritis and nephrosclerosis on the basis of glomerular obstruction and the resultant ischemia and atrophy of the attached tubule.[2] Recently, however, in aged persons many direct arterial communications with the postglomerular circulation have been found,[1] and in chronic renal disease it has been shown that glomerular patency is not necessary for an efficient circulation of blood through the peritubular capillaries.[3–5]

Oliver and his co-workers[3] have demonstrated that direct arterial connections with the peritubular capillaries appear in larger and larger numbers as glomerular damage increases. These communications spring from the arcuate and interlobular arteries and from the afferent arterioles. The latter types appear to be of special importance. First observed by Isaacs in this country and later by Ludwig, they have come to be called Isaacs–Ludwig arterioles or simply Ludwig's vessels.[6] A Ludwig vessel comes off the afferent arteriole perpendicularly or obtusely and straightway enters the tubular capillaries by-passing the glomerulus. Preceding the development of this collateral circulation there is thickening of the basement membrane, proliferation of extracapillary connective tissue and capillary endothelium and an occlusion of glomerular capillary loops.[3] Additional obstruction to flow of blood through the glomeruli has been attributed to deformation of the corpuscle by the overgrowth of interstitial elements, and by hypertrophic or hydronephrotic tubules.[3] When amyloidosis is the cause of chronic renal disease, amyloid material may be found about the cells of the subintimal layers,[7] at first in discrete deposits, which later coalesce to produce rigidity and luminal narrowing and, in

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the glomerulus, occlusion of the loops. In addition, the capillary networks become thicker and the large vessels are more sharply defined by parietal changes, until the parenchyma of the kidney seems to rest upon a scaffolding of numerous relatively rigid vessels.[8] In all types of chronic renal disease intimal thickening and deposits of lipoidal material contribute to vascular rigidity. Vessels may be formed *de novo* but mainly seem to be derived from preexisting channels. Thus, after infarction the newly appearing collateral vessels arise largely from a remodeling of those already present.[9] Spanner[10] doubt that certain unusual cells appear among the myocytes in the media of renal arteries and arterioles and are particularly numerous close to the junction of the afferent arterioles and the malpighian corpuscles in mice, rats, dogs, cats, rabbits, ferrets and man.[11] They are, however, variously described, and it is questionable whether they are identical structures in the various species and whether more than one type occurs. Close to the glomerulus (Fig. 1) the internal elastic membrane may disappear and the media may be replaced by a thick sheath of cells, somewhat larger than myocytes,

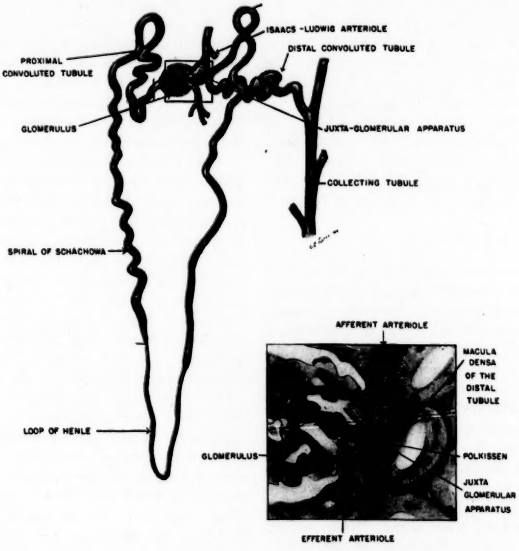

FIGURE 1. *Schematic Representation of a Typical Human Nephron Showing the Important Structures.*

The juxtaglomerular apparatus and the macula densa of the distal tubule are shown in greater detail at the lower right.

has demonstrated arteriovenous anastomoses anatomically in the human kidney, and it has been suggested that retrograde perfusion of the peritubular capillaries through these structures may follow glomerular obstruction. Activity of these anastomoses, however, has not been observed in chronic disease,[8] and they appear to be completely lacking in infarcted areas.[9]

Juxtaglomerular Apparatus

Interpretation of the histologic structure of the afferent arteriole remains as confused as it was when Smith[6] reviewed the subject at some length in his Harvey Lecture of 1939. There seems to be little that have a clear cytoplasm in which acidophilic granules may or may not be found. In the human kidney these granules may be fluorescent.[12] The cuff pouts out eccentrically at the point of junction with the capsule to form a polar pad (*Polkissen*) closely attached to a segment of the distal convoluted tubule. The distal tubular segment at this point shows crowding and increased height of the epithelial cells, the macula densa. The argument concerning the identity of the medial cells appears to revolve about the presence and character of granules that were absent in the cells of the *Polkissen* described by Zimmermann[13] but present in the "epithelioid cells" described in the media by Ruyter,[14] Oberling[15]

and Goormaghtigh[16]; they are large and striking in the mouse but small and inconspicuous in man. After further study this conflict may be resolved on the basis of the differences in species and of the various histologic methods employed. A number of workers have been struck by the resemblance of these cells to the "epithelioid cells" that invest the vessels in the normal glomus and appear so strikingly in glomus tumors.[17] It is usually stated that these cells have a clear cytoplasm. Zimmermann[13] denies that the cells observed by him were epithelioid in character and observed fine fibers that passed through the cytoplasm. He did, however, describe "pericytes" about the glomerular capillaries — cells apparently derived from the smooth muscle and capable elsewhere in the body of regulating capillary flow. Murray and Stout[17] have recently shown that epithelioid cells from glomus tumors take on, in tissue culture, all the characteristics of the typical pericytes of Zimmermann. Hence, the possibility remains that the cells in question represent an intergrade in the transition between the smooth-muscle cells of the media of the afferent arteriole and the pericyte of the glomerular capillaries.

Goormaghtigh[16] has named the structure at the terminus of the afferent arteriole the "myoneuro-arterial juxtaglomerular apparatus." Its description is germane to the present discussion because of the view expressed by Goormaghtigh[18, 19] and others[20, 21] that the structure is an endocrine organ, the probable site of renin formation. Opposed to this is the notion, based on the resemblance of the structure to glomic cells found at arteriovenous anastomoses in the digits and elsewhere, that it regulates the flow of blood through the glomerulus in response to nervous stimulation of the thick neural net associated with it, and to chemical stimulation of the macula densa by the urinary constituents.[15, 22] The first hypothesis is supported by the finding of Goormaghtigh and Grimson,[23] confirmed by Graef,[6, 11] that hypertrophy of the structure occurs during experimental renal hypertension and by their further finding, confirmed by others,[20, 21] that hypertrophy of this structure occurs in essential hypertension, nephritis and eclampsia. Oberling,[22] however, failed to find such hypertrophy frequent in hypertension but, on the contrary, noted degeneration and regression. He believes that the lesions described by Goormaghtigh are the result of hypertension and represent muscular hypertrophy and arteriosclerosis. Moreover, such hypertrophy is usually not striking or uniform, and it is an admittedly uncommon finding.[19] The second suggestion lacks any supporting evidence, although an abundant innervation of the structure has been demonstrated.

Recently a singular case was reported by Graef[24] in which hypertrophy of afferent arteriolar medial cells presented the only pathological evidence of renal disease. The patient, a woman of thirty, suffered from hematuria, proved to be unilateral. In the third month of pregnancy nephrectomy was performed on the basis of a diagnosis of renal neoplasm. The excised kidney appeared grossly normal, but microscopic examination revealed a striking change in all the arterioles, consisting of hypertrophy and hyperplasia of the medial cells with luminal constriction. These changes were especially marked at the point of entrance of the afferent arteriole into the glomerular network, where the hypertrophic changes were so extensive as to indent the glomerulus and surrounding tubules. All the cells were granular, and the cytoplasm was quite clear. Erosion of the pelvic and ureteral epithelium appeared to account for the hematuria. The subsequent course of this patient was of significance, for after an uneventful postoperative recovery, toxemia of pregnancy appeared in the ninth month of gestation, with proteinuria, hypertension, convulsions and coma. Recovery followed spontaneous delivery of a stillborn child. Hypertension continued to be present during the succeeding month and then the blood pressure returned to normal. Graef suggests that hormonal activity during pregnancy may be responsible for a change in vascular smooth muscle similar to the change in the myometrium.

Interstitium

In all forms of Bright's disease, active and passive alteration of the renal interstitial tissue is prominent. The disappearance of nephrons creates dead space filled by connective tissue, usually with thickening of the stroma by shrinkage rather than by proliferation. In addition to this passive increase in stroma there may be an active process of fibrous-tissue proliferation, probably in a large part secondary to inflammation, evident pathologically by the cellular infiltration. This is most profound in pyelonephritis or, as Bell[25] calls it, "exudative interstitial nephritis," where bacteria may be found exciting an inflammatory response to the point of abscess formation with sequential fibrous-tissue proliferation.[26] In glomerulonephritis, inflammatory changes ranging from edema and polymorphonuclear infiltration to fibroblastic proliferation with collagen formation and round-cell infiltration may be observed.[3] The normally thin sheets of fibrous tissue are widened to thick bands, which may at first increase the bulk of the organ but later cause shrinkage by destruction of the nephrons. The fibrillae are obviously newly added for they are irregular and disoriented and soon enmesh tubules and glomeruli, producing by constriction all degrees of atrophy and distortion.[3] It seems clear that here, as in pyelonephritis, the interstitial inflammatory reaction precedes any serious modification of the renal parenchyma. In the kidney of the hypertensive, however, where vascular changes are predominant early in the course of the disease, the in-

terstitial modification is fairly simple and is mainly secondary to parenchymal shrinkage, with approximation of fibrils causing increased density.[3] Inflammation is seen frequently enough, however, in the hypertensive kidney to sustain the belief that here, too, it contributes to the interstitial disorder.[3, 27] Terminally, in all, if the course is protracted, granulations of the surface appear where connective tissue collapses and contracts about still viable nephric units, which may be greatly hypertrophied, while the kidney becomes small and misshapen.

Parenchyma

The three dimensional reconstructions of renal micromorphology in Oliver's laboratory[3] have thrown new light on nephron structure in disease. It has been shown that pathologic nephrons may be broadly divided into two categories, the atrophic and the hypertrophic.[28] The *hypertrophic* nephron shows a striking change, almost entirely limited to the proximal tubules, which may be increased in bulk as much as ten times the normal. Cellular hyperplasia, luminal dilatation and increased length, especially marked in the terminal broad segment, the so-called "spiral of Schachowa," with displacement of Henle's loop, account for the increase in size. The distal tubule may be normal or may show evidences of other types of pathologic change. The *atrophic* nephron exhibits an irregular diminution in the size and number of the tubular cells. This may be associated with dilatation or stenosis. Of course, there is a considerable degree of intergrading so that hypertrophy and atrophy may appear side by side in the course traced by the tubule through the kidney, or the degenerative change may be so extreme as to lead to destruction of the walls and fragmentation of the tubule. Disruption often occurs close to the glomerulus in the proximal convoluted tubule and is followed by healing with the formation of aglomerular nephrons and atubular glomeruli. Either may persist long after the remainder of the unit to which it was formerly attached has completely disappeared. The aglomerular tubule may be otherwise entirely intact and show all the possible changes of atrophy and hypertrophy. Fragmentation may result in the formation of islets of tubular tissue that appear as clusters of cells or, more frequently, as small cysts filled with hyaline material.[3]

Vascular pathology and interstitial tissue proliferation are major causes of the lesions, but other factors may be equally important. Agents capable of both damaging and stimulating the renal parenchyma may manifest themselves by decreases in mitochondria,[29] deposits of lipoidal material, cloudy swelling and even severer changes leading to cell death on the one hand and by increases in nuclei and hypertrophy of cells on the other. Many of these cellular changes may precede significant ischemia or fibrosis. It is probable that unidentified toxins are concerned in glomerulonephritis, pyelonephritis and certain of the nephroses. To what extent associated endocrinopathies may contribute to this is unknown. It is certain, however, that the appearance of large amounts of protein in the glomerular filtrate is accompanied by intracellular deposits of hyaline and lipoid material. Evidence based on chemical and electrophoretic studies of urinary protein suggests that the beta-globulin fraction of the plasma protein is largely responsible for the formation of hyaline casts and blockage of the tubules both in nephritis and in the renal failure of multiple myeloma.[30–32]

Intratubular casts that occlude the lumens and cause hydronephrotic changes cannot be neglected as a potent cause of tubule alteration.[3] Almost the total length of a tubule may be filled with solid substance. These consolidated masses seem to be clearly ante mortem in origin and not artifacts. Casts are usually heterogeneous conglomerates of solid material, granular or hyaline in appearance, probably derived from precipitated constituents of the glomerular filtrate and desquamated tubular epithelial cells; many contain red cells and leukocytes. In pyelonephritis the tubules are frequently packed with leukocytes enmeshed in a hyaline matrix.[26] Later the leukocytes disappear and many tubules, cyst-like in appearance, remain blocked with a bluish-staining colloid material. It is stated that such casts are distinctive and diagnostic of pyelonephritis.[33] Casts are found in the collecting tubules and distal convoluted segments, and granular material is occasionally seen in the loop of Henle, but the proximal segment usually remains empty. This finding is in accord with the view that concentration of the glomerular filtrate takes place in the distal tubule. Whether primary blockage occurs in the collecting tubules, — which are characteristically affected by the disease, causing kinking and coiling to trap the solid material, — or in the distal tubule is not settled, but it seems likely that, although it occurs more frequently in the former, than in the latter, obstruction of the distal tubules can occur.[3] Above the point of obstruction the tubule may dilate widely, and this dilatation may extend the full length of the tubule proximal to the block. The degree of structural alteration depends largely on the state of the stroma, which by constriction may cause the formation of varices, outpouchings or stenosis of the hydronephrotic tubules. The blocking cast may so fill out the distal segment as to encroach on and deform surrounding structures. The proximal convoluted tubule placed in close proximity to the distal segment may then be flattened to a ribbon, and the glomerulus, attached to the macula densa of the distal segment, may also be badly misshapen. The glomerulus is never dilated

by the hydronephrosis of tubular blockage. This has also been shown to be the case in the normal kidney deformed by hydronephrosis.[34]

* * *

Several important facts, therefore, have emerged from the recent studies of renal pathology, especially those of Oliver, whose monograph[3] should be consulted for further detail. First, the doctrine of glomerular dominance of the renal circulation is discredited by the finding of a gradual development of a predominantly tubular circulation through accessory vascular channels. Second, the role of the interstitial tissue in the renal deformation of chronic Bright's disease is reaffirmed and established. Third, hydronephrosis secondary to the obstruction of nephrons and collecting tubules is emphasized as contributing to the architectural deformity. Finally, the demonstration of hypertrophic units and of aglomerular tubules raises the question of the functional ability of these structures.

It seems reasonable to infer that hypertrophy and hyperplasia of renal structures indicate adaptive functional responses to increased demands resulting from a shrinkage in the total functional mass. Likewise, similar changes in aglomerular nephrons seem to indicate continued activity requiring secretion of water across the tubular epithelium. Since it is known that, in certain fish, aglomerular kidneys secrete urine, it has been suggested by Marshall[35] that a return to the more primitive state may occur in chronic renal disease. The demonstration of an increasing number of intact aglomerular nephrons in the kidney of Bright's disease[3] appears to substantiate this hypothesis. Functional evidence of the operation of such aglomerular units, however, is totally lacking.

Initial Patterns of Disease

Although the fact that all forms of Bright's disease converge on a common terminal pattern requires emphasis, it should be remembered that each form of the disease has a distinctive initial pattern. In glomerulonephritis, glomerular damage dominates the earliest stage. Endothelial proliferation blocks the glomerular capillaries, and thrombosis and occlusion by crescent formation are occasionally observed. Thickening, fusion and splitting of the basement membrane are followed by the appearance of intracapillary fibers. A widespread interstitial inflammatory reaction, an irregular dilatation of proximal tubules and occasionally small deposits of lipoid material in the tubular cells or in the vessel walls may be found. If healing occurs, these evidences of disease may be entirely removed, but if activity continues, the structural alteration usually becomes profound within one or two years. Oliver[3] is of the opinion that two types of chronicity are manifest. In one, atrophy, hydronephrotic dilatation and disruption of tubules, and glomerular obliteration are predominant; in the other, extensive tubular hypertrophy and hyperplasia with vascular readjustments occur. He attributes the former to a continuously active disease process, and the latter to remittent activity of the disease process, during which recuperation and compensatory renal changes take place.

In the nephrosclerotic kidney is found a very different pattern, consisting of arterial and arteriolar sclerosis and little interstitial inflammation. The small arterial branches are always the more severely involved, showing tortuosity and fatty deposits in the walls. Hyperplasia of the endothelium is frequently seen in small arteries and large arterioles and is usually "associated with medial degeneration (intracellular collagen and thinning) and in many instances complicated by hyaline, fat, mucoid or chromotropic degeneration, or necrosis of the hyperplastic intima as well as of the media." [37] Hyalinization of the afferent arteriolar intima often occurs. Interstitial fibrosis is evidenced at first by the formation of a few scars; later it is diffuse, with the destruction of the greater part of the cortical tissue. The tubules show atrophic changes within the scar and hypertrophy outside it. In the accelerated form of the disease (malignant nephrosclerosis), extensive and complete occlusion of the tubules and marked hydronephrotic changes are widespread. In addition, variable changes in any one nephron, such as hypertrophy and atrophy, are of common occurrence. Necrosis of the wall of the afferent arteriole may be found, with contiguous inflammation of the surrounding interstitium.[27]

The nephrotic kidney shows relatively little change in its architecture, even though numerous casts may fill the tubules and disruption may occur. Depending on the etiology a heavy lipoidal deposit in the tubular epithelium may be found.

In acute pyelonephritis, focal accumulations of polymorphonuclear leukocytes appear throughout the kidney, about venules and capillaries plugged by bacterial emboli or about glomeruli.[25, 26] These accumulations may develop into multiple abscesses destroying and replacing local structures. Following release of the obstruction to urine flow in the experimental animal, and possibly in man, regression occurs, the lesions are resolved and a diffuse interstitial fibrosis sets in, which damages nephric units not previously affected by the disease.

Terminus and Differential Diagnosis

It is not unusual for renal disease to become clinically manifest only when the kidney fails, and it is precisely at this stage that differential diagnosis is particularly difficult because few distinctive pathological or clinical features may stand out. Since the processes involved in the disorganization of renal structure are common to all types of Bright's disease, it is not surprising that convergence from initially specific patterns on a terminal similarity

of structure and function occurs. Mansfield, Mallory and Ellis[38] have considered this problem in 59 patients dying in uremia at the Boston City Hospital in whom the diagnosis was made on pathological grounds. In these cases no pathognomonic pattern of clinical or laboratory findings could be discerned. It was thought, however, that a diagnosis should be attempted although frequently it could be reliably based only on a knowledge of the natural history of the disease. In many cases this information may be lacking and diagnosis must be tentative. Pathological diagnosis is usually less difficult but even then differentiation may be controversial. These facts are evident in the confusion in the literature regarding pathological differentiation of chronic and healed pyelonephritis from the other forms of chronic Bright's disease. Mansfield and his co-workers[38] quote unpublished data of Kinney and Mallory as indicating evidence of healed pyelonephritis in almost 14 per cent of all autopsies. On the contrary, Shure[39] found pyelonephritis in only 2.44 per cent (290 cases) of 11,898 post-mortem examinations and Bell[25] records an incidence of 2.47 per cent (808 cases) in 32,360 autopsies, of which only 64 cases were nonobstructive in origin. The great discrepancy in these figures can be attributed in part to a failure to establish uniform standards of diagnosis. Bell[25] and others[40, 41] who have recently reviewed the literature reject pyelonephritis as an important cause of hypertension. Further studies are necessary to determine the relative importance of pyelonephritis and of chronic diffuse glomerulonephritis in causing renal failure.

(To be concluded)

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Weekly Clinicopathological Exercises

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CASE 30381

PRESENTATION OF CASE

A forty-nine-year-old housewife entered the hospital because of jaundice.

The patient was in apparent good health until about one and a half years before admission, when she had an attack of pain in the right upper quadrant radiating to the right shoulder blade. There was no jaundice. X-ray examination at a hospital in another city was said to be negative. About six months before entry she had another attack of pain in the right upper quadrant associated with slight fever and jaundice that lasted for one month. The stools were clay colored, and the urine was positive for urobilinogen. X-ray examination showed the gall bladder to be poorly visualized. The patient was well again until seven weeks before entry, when she became jaundiced and the stools were clay colored. She had pruritus but no pain until the week of admission, when she began to have intermittent pain in the right upper quadrant accompanied by discomfort in the right flank and some pain in the right scapula. She was seen by her physician who found urobilinogen in the urine and a normal galactose-tolerance test.

The past history was negative except for a history of herpes zoster about two years before entry.

Physical examination showed a well-developed and well-nourished, jaundiced woman. The heart and lungs were normal. The abdomen showed no spasm, tenderness or masses. Murphy's sign was absent.

The blood pressure was 170 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 13,400. The hemoglobin was 12 gm. per 100 cc. The urine was normal. The serum bilirubin was 12.1 mg. per 100 cc. direct, and 14.8 mg. indirect. The prothrombin time was 18 seconds (normal, 18 to 20 seconds).

The patient was given 4 mg. of hykinone twice a day intramuscularly and on the third hospital day an operation was performed.

*On leave of absence.

DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK: The late Dr. E. P. Richardson was credited with saying that one could make a diagnosis of gallstones in three minutes or one could not make it at all. I think he was right. I do not know what the diagnosis was in this patient. There is not evidence enough on this record, and I presume that the patient did not present evidence enough to make it possible for me to make a diagnosis that I am happy with. I should have liked to have a little more information from the patient, just to clear up one or two things in my own mind. I should have wanted to know more about the attack of pain one and a half years before entry. How severe was that pain? Was it a definite and severe enough attack so that it would have meant gallstones to me?

DR. BENJAMIN CASTLEMAN: The opening sentence in the original record reads, "The patient out of a clear sky had an attack of pain in the right upper quadrant, with radiation into the right flank and in the region of the right shoulder blade."

DR. MCKITTRICK: But we want to know whether she had to bend over, whether the pain was extremely severe, whether she walked the floor — those are little points on which one makes a diagnosis. Was she perfectly well between the attack of a year ago and the one six months ago and until the onset of the jaundice seven weeks ago? I should like to be more clear in my mind about these things. The attack certainly in location and distribution is typical of biliary colic. The second attack, with fever and jaundice, was apparently consistent with a stone in the common duct, and the third attack was not at all typical. Therefore, I cannot make a diagnosis that satisfies me. I shall start with that premise and take the case up from another point of view and see what I can do.

The first thing is to try to decide whether this was an intrahepatic or an extrahepatic jaundice. In other words, did this woman have a hepatitis of some type or another or some extrahepatic pathology, such as gallstones, stricture of a duct or carcinoma in relation to the duct or the head of the pancreas? I cannot even make that differentiation clearly. There are certain things that suggest one thing, and some another. The urobilinogen does not mean much to me. I believe that urobilinogen is not found in the urine in a straight case of obstructive jaundice, except in the early stages, when there may still be bile in the intestinal tract that may be absorbed. It is likelier to be found in the urine in cases of liver damage. Is that correct, Dr. Beckman?

DR. WILLIAM BECKMAN: Yes.

DR. MCKITTRICK: The normal galactose-tolerance test offers some evidence against severe intrahepatic disease. The prothrombin time was normal. There is some suggestion that if the patient did have

hepatitis she did not have extensive liver destruction. Seven weeks of complete absence of bile from the stools, I presume, is a reasonable length of time for the average case of hepatitis to go on. It may not be too long, but is long enough so that one should begin to feel uneasy about it.

This woman had two attacks of pain that I should try to link up with the final diagnosis, but I must confess that at this moment I am not sure that I can do it in a logical manner. I am certain that the important decision to make is whether the patient had a surgical or a medical jaundice. Could one make a diagnosis of intrahepatic disease with sufficient accuracy to say that the patient should not have been operated on? That I cannot do. I believe that it was a surgical jaundice, not because I have strong conviction that it could not have been intrahepatic, but because she had two previous attacks of pain and for seven weeks had acholic stools. Having decided in my own mind that the patient should have been operated on, I should try to clarify in my mind — and the family also would have liked to know — what I thought that I was operating for, whether for gallstones or a carcinoma of the duct, or the head of the pancreas.

This patient had had two previous attacks of pain. When a patient has had two such attacks, it seems to me that the question of gallstones cannot be excluded, no matter what the rest of the picture indicates. This patient did not present the classic picture of carcinomatous obstruction to the common duct, that is, the triad on which I place a great deal of importance — progressive and painless jaundice and a palpable gall bladder. The jaundice had progressed for seven weeks, and there was no pain at the onset of the jaundice, but the gall bladder was not palpable.

What about gallstones? Could gallstones give an attack of jaundice without pain? Of course they can. The mere fact that she had had two previous attacks of pain, one of which was associated with jaundice, is considerable evidence in support of the possibility that gallstones were present. On the other hand I think I am correct in saying that we do not see many women forty-nine years of age with a gallstone history dating back only one and a half years, during which time they have had only two attacks, in whom an attack due to a common-duct stone is initiated with painless jaundice. The biliary setup that usually gives painless jaundice is the contracted gall bladder where the stone has been squeezed down into the common duct and has settled down in the ampulla. This particular setup generally occurs in cases with long-standing biliary-tract disease and is infrequent.

It seems to me that we are left trying to put together from this bit of confusing evidence a reasonable diagnosis. I believe, although I have no strong conviction about it, that this jaundice was of extrahepatic origin. I must make a diagnosis of gallstones, although I am not happy about it. If I had talked with this patient, I believe that I should have found out something about these attacks of pain that would have clarified them in my mind. All I have to go on is the location, the sudden onset and the radiation. In the presence of a story of that sort I must make a diagnosis of gallstones.

Then the question comes up, If gallstones were present, were they the cause of the most recent attack? The mere fact that she had gallstones does not mean that she was being operated on for a condition secondary to the presence of such stones. Six months is a long time to go between attacks due to a stone in the common duct. Usually the attacks become more and more frequent as the stone gets into the common duct.

I could talk the rest of the day and not be any nearer to a definite diagnosis. I had better stop. I think, without conviction, that this was an extrahepatic condition. I will make a diagnosis of gallstones but I am not sure whether the obstruction, the cause of the jaundice, was a stone in the common duct or carcinoma related to the ductal system or possibly to the head of the pancreas. So long as one has to put one diagnosis in front of the other, and rather than make two diagnoses, I will say that I favor a diagnosis of gallstones, with a stone impacted in the ampulla.

DR. MAURICE FREMONT-SMITH: The fact that she had one episode of jaundice and clay-colored stools, without pain, is additional argument for stone, is it not?

DR. MCKITTRICK: It is a good logical course of events, but on the other hand, it is so good that I am suspicious. I am a little upset by the long interval — six months — between the second attack of pain and the development of painless jaundice.

DR. LLOYD MILLS: Regarding painless, progressive jaundice, a recent statistical survey of carcinoma of the head of the pancreas indicates that over 50 per cent of the patients had pain at some time during the course of the disease and that a smaller percentage had intermittent rather than progressive jaundice.

DR. MCKITTRICK: I shall answer that in a different way. Whenever there are variations, one has to be careful of conclusions. When one has a patient, however, who says that the family noticed that her eyes were yellow and she becomes more and more jaundiced, that jaundice was not initiated with an attack of pain — in other words, the jaundice was painless. If these two things happen and one can palpate a large smooth gall bladder, they nearly always mean a malignant obstruction to the common bile duct.

CLINICAL DIAGNOSES

Chronic cholecystitis.
Cholelithiasis?

Dr. McKittrick's Diagnoses

Cholelithiasis.
Choledocholithiasis?
Carcinoma of common bile duct or head of pancreas?

Anatomical Diagnoses

Adenocarcinoma of right hepatic duct, with extension into the entire common duct.
Cholelithiasis.
Chronic cholecystitis.

Pathological Discussion

Dr. Castleman: At operation the surgeon removed a thickened distended gall bladder; the right and left hepatic ducts and the common duct were markedly distended, being two or three times the normal diameter. After the cystic duct was clamped and compressed in such a manner as to force its contents into the common duct, the common duct was opened and a cast of the duct composed of greenish-black, rubbery, tissue-like material was pulled from the entire common duct. Similar material was suctioned from both hepatic ducts. I was called to the operating room and shown this material. The outside was coal black, but the inside was a mottled pinkish red and looked like definite tissue. A frozen section proved it to be an adenocarcinoma. The surgeon was able to scoop out this material easily because it was not adherent. The origin of the tumor was believed to be in the right hepatic duct, because its wall was thicker and rougher than the rest of the duct. There were no definite stones in the common duct, but the gall bladder had small blackish stones. I suppose that stones had been passing through the common duct for some time. A T-tube was placed in the common duct.

Dr. McKittrick: Was the ampulla patent?

Dr. Castleman: Yes.

Dr. Laurence L. Robbins: A postoperative cholangiogram shows a constant defect in the right hepatic duct.

Dr. McKittrick: That makes a perfectly good story. She could have had a hemorrhage from the tumor, and the blood could have passed down and caused an attack of pain the same as that of gallstones. The only reason that one says gallstones is that there is not much else in the biliary tree, except gallstones, to give attacks of pain. The last attack of jaundice can be explained by the propagation of this tumor mass down the common duct and gradual occlusion in that way.

Dr. Castleman: Do you think anything more can be done surgically?

Dr. McKittrick: No; it is a difficult area to approach.

CASE 30382

Presentation of Case

A forty-seven-year-old married woman was admitted to the hospital in semicoma.

Because of the patient's stuporous state only a meager history was obtainable from relatives and her private physician. About five months prior to admission she first noted some rectal bleeding, which continued intermittently. The amount and color of the blood could not be ascertained. About six weeks before entry she developed lower abdominal pain, which became progressively severer and was associated with increasing constipation. For about four days prior to entry she was unable to move her bowels although she had a frequent and intense desire to do so. A physician was called and prescribed 0.02 gm. of pantopon every four hours. This regimen was followed religiously except when the patient slept. During the twenty-four hours before admission she became stuporous and ceased to void and during that time she received only 0.02 gm. of pantopon.

The patient had gonorrhea twenty years prior to admission and was treated for a year. About a year later she had an attack of redness and swelling of the knees and the joints of the feet, which cleared up after bed rest. Twelve years before entry she had attacks of vomiting and pain in the right upper quadrant, following which a cholecystectomy, choledochostomy and routine appendectomy were performed, with relief of symptoms. A few small stones were found in the gall bladder and one was removed from the common duct. At that time several urine examinations revealed a specific gravity ranging from 1.018 to 1.032, with no albumin and a sediment containing numerous white cells, occasional red cells and a rare cellular cast. For about ten years before admission she had had nocturia two to four times.

Physical examination revealed an obese woman in semicoma, breathing stertorously. She responded to shaking but not to painful stimuli. The pupils were very small, round, regular and equal, and there was only slight reaction to light. The mouth and tongue were dry. There was a uriniferous odor to the breath, and a uremic frost was noted. The lungs were clear, and the heart, except for a rapid rate, was negative. The abdomen was moderately distended and there was slight tenderness to deep palpation in the lower portion. The deep tendon reflexes were active and equal, the abdominal reflexes were absent, and the Hoffmann and Babinski signs were positive. Pelvic examination revealed a prolapsed and lacerated cervix, but no masses could be felt in the vaults. Digital examination revealed a firm, rather smooth, fixed mass on the anterior wall of the rectum about 8 cm. above the anus; a small

amount of bright-red blood stained the examining finger.

The temperature was 98.6°F., the pulse 100, and the respirations 18. The blood pressure was 120 systolic, 75 diastolic.

Examination of the blood revealed a red-cell count of 4,000,000, with 70 per cent hemoglobin, and a white-cell count of 24,400, with 86 per cent neutrophils. A catheterized urine specimen had a specific gravity of 1.010, with an acid reaction, a +++ test for albumin and 10 white cells per high-power field; no sugar or acetone was present. The blood nonprotein nitrogen was 130 mg. per 100 cc., the serum protein 6 gm., and the chloride 89 milliequiv. per liter. A Hinton test was negative. Roentgenographic examination of the abdomen was unsatisfactory; it revealed considerable gas in the cecum and sigmoid, but no definite dilated loops of small bowel could be seen. An electrocardiogram was within normal limits. A biopsy of the rectal mass revealed adenocarcinoma.

Following admission the patient was catheterized and a considerable amount of pale urine was obtained. A lumbar puncture revealed clear fluid with normal dynamics. The respirations fell to 10 per minute, and she was treated with picrotoxin, receiving 14 mg. over a period of six hours, followed by inhalation of carbon dioxide. There was temporary improvement for several hours, but the respirations soon fell to their former level. On the third hospital day the ureters were catheterized. The catheters were passed with ease but no urine was obtained. Fluids were administered intravenously up to 2500 cc. daily, principally dextrose in water and some sodium lactate. By the fifth hospital day she had begun to void, her sensorium became clearer and her respirations had increased to 16 to 20 per minute. The ureteral catheters were then removed.

In spite of a fair urine output and apparent improvement enabling the patient to sit out of bed for short periods, the nonprotein nitrogen continued to rise, eventually reaching 235 mg. per 100 cc. The blood carbon dioxide content was 17.5 milliequiv. per liter. The blood pressure on several occasions reached 190 systolic, 110 diastolic, although it was usually lower. On the eighth hospital day a difference in the circumference of the two legs was noted. Homans's sign was negative. A prophylactic superficial ligation of a leg vein was done. On the following day the urine was red and cloudy, with a specific gravity of 1.010, an alkaline reaction, a ++++ test for albumin and a sediment containing innumerable red cells and many white cells but no casts.

The patient's condition rapidly became worse. On the fourteenth hospital day she again became anuric and 25 per cent glucose and plasma were administered intravenously in a vain attempt to induce diuresis. The blood pressure fell to 120 systolic, 60 diastolic, and she vomited frequently. Gastric lavage produced 750 cc. of bloody fluid, and she was placed on constant gastric suction. She died on the fifteenth hospital day.

Differential Diagnosis

Dr. Austin Brues: In this case we are presented with a pathological diagnosis of adenocarcinoma, apparently of rectal origin. This accounts well for the rectal bleeding and for the progressive constipation and abdominal pain. For the rest, it is necessary to establish the cause of the patient's anuria, uremia and death.

The first thought that naturally arises is that this terminal picture might have been due to extension of the malignant tumor. It is an interesting fact, however, that death by renal failure is a very rare complication of cancer of the lower bowel, in contrast to cancer of the cervix and of the urinary tract itself. Metastasis from rectal carcinoma characteristically goes to lymph nodes and to the liver via the portal venous system, and spares the urogenital tract. We have no evidence to suggest that the pelvic tumor was large enough to compress both ureters, and finally, it is stated that catheters could be passed easily through both ureters. We are forced to conclude that the urinary suppression was of renal or prerenal origin.

What evidence do we have regarding the possibility that the patient had chronic renal disease? Twelve years before entry, at the time of the gallbladder operation, several urine examinations showed abnormal sedimentary findings, including red cells but no albumin. Also, for ten years before admission she had had nocturia. Unfortunately, we do not have a record of her blood pressure at any time prior to admission in coma, nor is there an examination of the eye grounds recorded. Either of these might have given us information whether this episode occurred in the course of chronic nephritis. Without them, we can only say that the history is suggestive of chronic renal disease which might or might not have been severe.

Assuming that the patient had indeed suffered from chronic glomerulonephritis or from chronic vascular disease with emphasis on renal impairment, what precipitated the present acute and fatal episode? Two possibilities stand out. This may, in the first place, have been an acute exacerbation — an acute hemorrhagic nephritis punctuating the course of chronic nephritis. It is perfectly possible, although not frequent, for acute nephritis to manifest itself by acute complete urinary suppression. In such a case the blood pressure would at first be normal, in the absence of chronic nephritis with hypertension, but this denies the first postulate, and we should have to minimize the chronic nephritis in favor of acute nephritis *de novo*. Moreover, when urinary flow was obtained, the urine was at first clear. The hypothesis of acute nephritis with or

without a previous renal background is not wholly satisfactory.

It seems to me that the case of a patient who is admitted in coma following dosage with pantopon, shows signs of morphine toxicity, and who at the same time develops fatal anuria, ought if possible to be explained on the basis of the drug. Sufficient doses of morphine depress blood pressure, and secondarily cause decrease or disappearance of urinary flow. The patient, however, had a normal blood pressure on admission. It is possible that she may have previously suffered from marked hypertension, although the clinical examination of the heart and the electrocardiogram do not suggest this, and that secretion of urine ceased when the blood pressure was brought down to a normal level, just as it may when the blood pressure of a normal person goes to shock levels. The second episode following vein ligation, on the other hand, being ushered in by hematuria without casts, suggests acute renal disease of some sort. Perhaps the previous ureteral instrumentation was responsible for the gross hematuria.

If this patient had received an earlier course of sulfonamide therapy, with dosage again just before admission, and perhaps again at the time of vein ligation, it would seem to me that this was a clear case of renal shutdown on a sulfonamide-sensitivity basis, and that we might expect to find inflammatory and granulomatous interstitial lesions in the kidneys. If she did get sulfonamides, however, this has been forgotten. Other drugs have occasionally been mentioned as factors causing anuria, and sensitization to opium derivatives, as evidenced by skin eruptions, does occur. Morphine has not to my knowledge been implicated in a picture such as this. We have nothing else in this case to suggest sensitization, such as skin rash, eosinophilia or fever. We do not even know for certain that morphine was given at the time of the vein ligation, although it probably was, the procedure being done under local anesthesia. The sequence of events and the lack of an entirely satisfactory diagnosis, however, tempt one to entertain such a thought.

Other causes of anuria, such as massive renal infarction, seem to have little to offer in this case. Extensive liver metastasis from rectal carcinoma might cause hepatic failure, with a high nonprotein nitrogen because of elevated amino nitrogen, and might interfere with the detoxication of morphine. I do not gather from the history that such unusually massive hepatic metastasis occurred, and we should still have to explain the anuria.

Clinical Diagnoses

Carcinoma of rectum.
Renal insufficiency, with uremia and anuria.

Dr. Brues's Diagnoses

Adenocarcinoma of rectum.
Chronic and acute glomerulonephritis?
Acute interstitial renal disease, sensitization type?

Anatomical Diagnoses

Acute pyelonephritis, with multiple small abscesses.
Chronic vascular nephritis.
Cardiac hypertrophy, hypertensive type, moderate.
(Uremia.)
Cystitis, acute and chronic.
Adenocarcinoma of rectum, with metastases to liver.

Pathological Discussion

Dr. Benjamin Castleman: The rectal carcinoma was located just below the rectosigmoid junction, and several small metastatic nodules were present in the liver. As Dr. Brues predicted, there were no metastases in the region of the ureters and no ureteral obstruction was apparent.

The kidneys together weighed 200 gm., the right a little heavier than the left. The capsules were thickened and adherent. The parenchyma was fairly soft, and the cortical and medullary markings were difficult to visualize. The cortex was somewhat narrowed and several yellowish-brown pin-point areas were present. Microscopically there was evidence of old vascular disease, especially of the arterioles, with hyalinization of a relatively small number of glomeruli. The remaining glomeruli appeared normal, and there was very little tubular atrophy or tubules filled with colloid casts, which should rule out chronic glomerulonephritis and chronic pyelonephritis, respectively, as the cause of the underlying renal disease. Superimposed on the chronic vascular nephritis was an acute pyelonephritis characterized by multiple small abscesses filled with bacteria, by pus in the tubules and by a fairly extensive polymorphonuclear infiltration of the parenchyma. The ureters were not dilated or thickened. The bladder was moderately inflamed.

The cause of the acute pyelonephritis is not easy to explain. So far as we know, the patient had not received any of the sulfonamides, and the purulent rather than granulomatous character of the inflammation is rather against a sensitivity reaction. Although the bladder was moderately inflamed, I believe that the infection was hematogenous rather than ascending from the lower urinary tract.

The heart weighed 410 gm. and showed left ventricular hypertrophy.

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THREE SCORE AND TEN

The longevity of the American people, the statisticians of the Metropolitan Life Insurance Company* tell us, reached its all-time peak in 1942. In that year white girl babies reaching their first birthday had, on an average, seventy years of life ahead of them, exceeding by one year the biblically allotted three score and ten. Not until their fortieth birthday did white males achieve an average expectancy of thirty additional years, thus suggesting, although by no means proving, that Methuselah was a lady.

**Statistical Bulletin.* Metropolitan Life Insurance Company. Vol. 25, April, 1944. No. 4.

Actually, the figures of 1942 give us striking evidence of what improved living conditions have done for the race, since in that year the average length of life of all our people, white and colored, was practically sixty-five years, a gain of nearly sixteen years since 1900, when the average length of life was forty-nine years. The slow rise over earlier recorded expectations of life is, of course, a hundredfold and more.

The ladies have always been better insurance risks than have the gentlemen, even in the lush years of peace and plenty. Since the turn of the century, for instance, the distaff side of the family has been granted an average increase in length of life of over seventeen years, as compared with the fifteen years accorded to the sterner sex; and even at the age of forty the remaining years for females have increased nearly five years, as compared with the miserly two and a half years increase allotted to the breadwinners of the families.

Among our colored population a noticeable improvement in life expectancy has also taken place, with an increase of nearly twenty-two years for males, and twenty-three years for females. But this substantial advance only brings the colored population up to a 1942 life expectancy of fifty-four years for males, and fifty-eight years for females — about the expectancy that the white population of this country had already achieved some twenty years earlier.

These figures, even as we realize that they are brought about largely by reductions in infant mortality and in the mortality of childhood, put a different and a more benign emphasis on the possibilities of a pleasant old age. The average person of sixty-five, for example, now faces the prospect of thirteen more or less pleasant years ahead and may even reach the age of eighty or more, if his health is above the average.

Some falling off in this expectation has taken place in 1943 and will continue in 1944 — years of stress and strain and overwork, and moreover years in which a minor epidemic of respiratory infections exacted an increased toll of lives. The future, however, if we consolidate our gains, holds out an increasingly pleasing prospect.

PNEUMONIA IN SHIPBUILDERS

THE recent tremendous addition to the number of welders engaged in essential war industries has brought into focus the possibility of an increase in respiratory diseases in such workers resulting from the character of their tasks. Symptoms of various sorts are attributed by these workers and by many physicians to the fumes to which they are exposed. The symptoms may simulate those of acute systemic or respiratory infections or those of chronic respiratory diseases. The former are encountered most frequently during the season when acute respiratory infections have the greatest incidence, which suggests an increased susceptibility of such workers to the prevalent infections. The latter are usually recognized in x-ray films of the chest taken routinely or because of respiratory symptoms.

With respect to the lung changes in electric-arc welders, Sander[1] has recently pointed out the importance of preventive measures for the protection of workers. He finds that electric-arc welding that is done in large rooms, or where the fumes are not allowed to concentrate excessively near the breathing level, does not cause lung changes even after many years of work. On the other hand, excessive inhalation of concentrated fumes, especially in confined and unventilated spaces, may cause siderosis. The siderosis so produced consists of the deposit of inert iron pigment in the lymphatics without fibrous-tissue proliferation and without progressive changes after the exposure is materially decreased. Sander also states that welding and siderosis do not predispose to tuberculosis or to other lung infections, nor do they cause functional impairment of the lungs or symptoms referable to the lungs. Acute irritations of the throat, however, may occur with too prolonged work in dense clouds of fumes, but these appear to be transitory and to leave no residual. He believes that any respiratory involvement may be prevented in welding, even with the most prolonged and confined work, if proper precautions are taken by installing adequate exhaust ventilation and by using ventilated helmets or positive-pressure respirators.

Another study, carried out by physicians of the Permanente Foundation Hospital[2] among the workers of the Kaiser Richmond Shipyards on the West Coast, suggests that acute pulmonary infections are neither more frequent nor more serious among shipbuilders than among similar persons in other walks of life. This study covered a twelve-month period during which 864 patients with pneumonia were treated. Some of the findings and the conclusions based on this study are worth mentioning.

The annual frequency rate of pneumonia at the shipyards was 9.5 per 1000 workers. This is probably a high incidence, but, as the authors point out, there are no reliable data to indicate that it is any different in shipyard workers than among the general population. It certainly is lower than the rate among certain types of workers in the iron and steel industries, but it is higher than the average incidence reported for all iron and steel workers.[3]

The type of pneumonia among the shipyard workers was in no way different from that among the general population. There was no indication that workers who had recently migrated to the region of the shipyards from other states were more susceptible to pneumonia than those who had lived in that region for a long time. The incidence rate for pneumonia was independent of the length of employment at the yards, as well as of the type of work done by the workers. In particular, pneumonia was no more frequent among welders than among those doing other jobs, such as laborers, electricians and machinists.

The gross mortality for the entire group of patients with pneumonia was 8.2 per cent. This figure, as the authors point out, compares favorably with that achieved in many of the best clinics throughout the country. A large proportion of the patients were over forty years of age and had more than one lobe involved. The mortality in patients under forty years of age was less than 4 per cent, and in those having only a single lobe involved it was less than 5 per cent. These low fatality rates suggest that the conditions to which the shipyard workers were exposed did not aggravate the prognosis in those who acquired pneumonia. More likely, however, it reflects the fine type of medical care that these patients received.[4]

Apparently the United States Maritime Commission has been deeply concerned about the widespread rumors among workers and physicians that

welding causes respiratory disease. The commission is, therefore, anxious to give the findings among the Kaiser shipyard workers widespread publicity in order not to discourage people interested in this form of employment.

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MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council of the Massachusetts Medical Society will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 4, 1944, at 10:00 a.m.

Business:

1. Call to order at 10:00 a.m.
2. Presentation of record of meeting held May 22, 1944. (Published in the *New England Journal of Medicine*, issue of July 27, 1944.)
3. Reports of standing and special committees.
4. Appointment of an auditing committee.
5. Fill any vacancies in the offices of the Society.
6. Such other business as may lawfully come before this meeting.

MICHAEL A. TIGHE, M.D., *Secretary*

DEATH

CRAWFORD — Francis X. Crawford, M.D., of Dorchester, died August 19. He was in his seventy-second year.

Dr. Crawford received his degree from Harvard Medical School in 1898. He was a member of the staffs of St. Elizabeth's and the Carney hospitals and a member of the American Medical Association.

His widow and four sisters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REIMMUNIZATION AGAINST TYPHOID FEVER

When a working basis for typhoid vaccination was established thirty-five years ago in the United States Army by Brigadier General (then Captain) F. F. Russell, the necessity for periodic reimmunization was recognized. At that time the policy of repeating the complete course of three doses of vaccine at three-year intervals was established. In recent years, the vaccination procedure as a whole has been extensively reinvestigated by the Typhoid Research Unit at the Army Medical Center. This group has found that adequate *reimmunization* can be obtained with a single dose instead of three doses of vaccine.

It is now well established that this single reimmunizing dose may be administered in one of two ways — 0.5 cc. subcutaneously or 0.1 cc. intradermally. Furthermore, it appears that this single dose is effective regardless of the interval since the last complete course of immunization.

The use of a single dose greatly simplifies the reimmunization process and also markedly reduces the incidence of local and systemic reactions, which are much more frequent and severe after reimmunization than during a first immunizing course.

The official recommendations are as follows:

(1) The administration of full courses of typhoid vaccine to persons who have previously been immunized against typhoid fever is unnecessary and should be abandoned.

(2) Wherever renewal of immunity is indicated in a previously vaccinated person, a single dose of vaccine should be administered.

(3) This dose should consist of 0.5 cc. subcutaneously or 0.1 cc. intradermally. Although there is evidence that intradermal injections are somewhat more effective than those given subcutaneously, it should be noted that the smaller dose is probably ineffective if it happens to be given subcutaneously instead of intradermally.

(4) The ideal interval between successive typhoid immunizations is one year, but a lapse of time greater than this between successive immunizations does not necessitate the administration of a full three-dose course of inoculations.

(5) Whenever there is doubt concerning the best immunization procedure to follow, it is suggested that the physician in charge consult one of the persons given below regarding the performance of a protection test on the patient's serum. This test, which can be done in four or five days at the Antitoxin and Vaccine Laboratory, is considered the best available method of determining a patient's immunity status.

The Director, Division of Biologic Laboratories
375 South Street, Jamaica Plain
(Telephone, ARNold 4127)

The Director, Division of Communicable Diseases
State House, Boston
(Telephone, CAPitol 4600)

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1944

RÉSUMÉ

Diseases	July 1944	July 1943	Seven-Year Median
Anterior poliomyelitis	23	1	4
Chancroid	1	*	*
Chicken pox	637	400	402
Diphtheria	14	6	9
Dog bite	1076	1115	1193
Dysentery, bacillary	23	2	11
German measles	60	468	60
Gonorrhea	356	355	355
Granuloma inguinale	1	*	*
Lymphogranuloma venereum	3	*	*
Malaria	66	12	1
Measles	876	1468	1159
Meningitis, meningococcal	32	51	5
Meningitis, Pfeiffer-bacillus	1	3	1
Meningitis, pneumococcal	2	5	†
Meningitis, staphylococcal	–	—	†
Meningitis, streptococcal	4	—	†
Meningitis, other forms	1	—	†
Meningitis, undetermined	1	9	†
Mumps	434	244	358
Pneumonia, lobar	86	93	147
Salmonella infections	11	19	9
Scarlet fever	246	439	261
Syphilis	303	363	409
Tuberculosis, pulmonary	233	191	288
Tuberculosis, other forms	19	17	23
Typhoid fever	2	6	5
Undulant fever	3	7	4
Whooping cough	284	317	521

*Made reportable December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

Comment

Anterior poliomyelitis, although showing a definite increase over the same period in 1943, does not indicate that epidemic proportions may be reached. It is impossible at this time to determine what the trend will be in the months ahead.

Mumps has shown an increase of almost 50 per cent over the corresponding period last year.

Dysentery has shown the usual seasonal increase.

Malaria has shown an increase, but the increase is primarily due to the return of service men from foreign fields.

The usual seasonal decline is noted in several of the diseases.

Geographical Distribution of Certain Diseases

Actinomycosis was reported from: Burlington, 1; total, 1.

Anterior poliomyelitis was reported from: Ayer, 1; Boston, 2; Camp Myles Standish, 1; East Longmeadow, 1; Hinsdale, 1; North Adams, 1; Pittsfield, 3; Quincy, 1; Springfield, 5; West Springfield, 6; Winchester, 1; total, 23.

Diphtheria was reported from: Boston, 4; Brookline, 1; Cambridge, 1; Lawrence, 1; Methuen, 3; New Bedford, 1; Revere, 1; Somerville, 1; Taunton, 1; total, 14.

Dysentery, bacillary, was reported from: Worcester, 11; Wrentham, 12; total, 23.

Hookworm disease was reported from: Framingham, 1; total, 1.

Malaria was reported from: Ashland, 1; Cambridge, 1; Camp Edwards, 11; Cushing General Hospital, 22; Fort Devens, 20; Gloucester, 1; Hanson, 1; Lynn, 1; Medford, 1; Milford, 1; Quincy, 1; Reading, 1; Somerville, 1; Springfield, 1; Waltham, 1; Winchester, 1; total, 66.

Meningitis, meningococcal, was reported from: Boston, 6; Braintree, 1; Chelsea, 1; Everett, 1; Fairhaven, 1; Grafton, 1; Haverhill, 1; Lowell, 2; Lynnfield, 1; Malden, 1; Melrose, 1; Methuen, 1; New Bedford, 1; Newton, 1; Pittsfield, 2; Quincy, 1; Revere, 1; Salem, 1; Saugus, 1; Shrewsbury, 1; Spencer, 1; Springfield, 2; Webster, 1; Worcester, 1; total, 32.

Meningitis, Pfeiffer-bacillus, was reported from: Tisbury, 1; total, 1.

Meningitis, pneumococcal, was reported from: Boston, 1; Dartmouth, 1; total, 2.

Meningitis, streptococcal, was reported from: Adams, 1; Barnstable, 1; Orleans, 1; Springfield, 1; total, 4.

Meningitis, other forms, was reported from: Cambridge, 1; total, 1.

Meningitis, undetermined, was reported from: Millbury, 1; total, 1.

Salmonella infections were reported from: Cambridge, 1; Dedham, 1; Lawrence, 1; Malden, 1; Methuen, 1; Salem, 2; Somerville, 1; Waltham, 1; Worcester, 2; total, 11.

Septic sore throat was reported from: Boston, 3; North Adams, 1; Quincy, 1; total, 5.

Tetanus was reported from: Springfield, 1; total, 1.

Trichinosis was reported from: Marblehead, 1; Norwood, 1; total, 2.

Typhoid fever was reported from: Boston, 1; Fall River, 1; total, 2.

Typhus fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Boston, 1; Hatfield, 1; Middleboro, 1; total, 3.

CORRESPONDENCE

INVENTORY OF DEMEROL

To the Editor: A form letter has recently been sent to all narcotic registrants relative to the substance isonipecaine, commonly known as "Demerol," which by a recent act of Congress has been brought under the provisions of the federal narcotic laws.

All registrants were called on to file an inventory with the Collector, not later than September 1, of Demerol on hand as of July 1. Many are under the impression that no inventory was required if they had no Demerol to report. This is not correct. In cases where registrants have no Demerol on hand, their inventory should so state. Those who failed to file on the required date should do so immediately. The original sworn copy is to be sent in to the Collector, and the duplicate retained.

Denis W. Delaney, *Collector*
Internal Revenue Service
Office of the Collector
Boston 9

CO-EXISTENCE OF GALLSTONES AND ULCER

To the Editor: In discussing one of the case records of the Massachusetts General Hospital (Case 30262) in the June 29 issue of the *Journal*, Dr. Wyman Richardson made the following statement: "The combination of gallstones and ulcer in the same patient is almost unheard of. . . . It is a striking thing that the ulcer habitus and the gallstone habitus are quite different, and I do not believe that I have ever seen the two diseases in the same patient." Since these cases are widely read, frequently quoted and generally considered authoritative, I believe the above quotation should be challenged.

Many years ago the Drs. Mayo emphasized an abdominal triad — appendicitis, gall-bladder disease and ulcer — in the same patient.

In 1931, Dr. Franklin W. White and I (*New Eng. J. Med.* **205**:793-797, 1931) reported a case of gastric ulcer and gallstones. Therein we stated, "The presence of gallstones naturally does not exclude ulcer; both may be present, in fact the association of lesions in the duodenum or stomach and the gall bladder is not at all rare." I am still subscribing to this view on the basis of my own experience and that of many others.

In 1943, Dr. S. A. Robins and I (*Am. J. Digest Dis. & Nutrition* **10**:445-447, 1943) quoted 3 patients who had had subtotal gastrectomy for intractable ulcers and later developed gallstones. I can also recall at least 2 patients who were operated for gallstones and showed at the accompanying exploration of the abdomen an active ulcer in the duodenum.

The day after I read the discussion of the above case I saw a patient who gave a twenty-year history of an ulcer. A duodenal ulcer was demonstrated by x-ray study in 1938 and again in 1944, and at the latter examination two large gallstones were also shown.

I have seen both in private and in hospital practice other cases in which a peptic ulcer and gall-bladder disease were present in the same patient. I have no records on hand to substantiate these cases, but I do not believe that it is necessary in view of the above facts.

I. R. Jankelson, M.D.
483 Beacon Street
Boston 15

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Medical Parasitology: A laboratory manual. By Jacques Yetwin, M.S., M.D., medical technologist and associate professor of parasitology, Middlesex University School of Medicine, Waltham, Massachusetts. Fourth edition. 8°, cloth, 126 pp., with 127 illustrations. Boston: Boston Linotype Print, Incorporated, 1944. $3.00.

This manual of a laboratory course has been modified to suit existing conditions brought on by the present war. The time allotted to the course has been increased from sixty to seventy-five hours. Mycology, as a rule, has been omitted, since it is taught in the course on bacteriology. The illustrations have been taken from a collection of five hundred slides of important parasites.

Baby Doctor. By Isaac A. Abt, M.D. 8°, cloth, 310 pp. New York: Whittlesey House, 1944. $2.50.

This autobiography of an eminent pediatrician who has practiced his specialty for fifty years naturally reflects the history and advances in pediatrics during that period.

Health and Hygiene: A comprehensive study of disease prevention and health promotion. By Lloyd Ackerman, Ph.D., Western Reserve University. 8°, cloth, 895 pp., with 59 illustrations and 27 tables. Lancaster, Pennsylvania: The Jaques Cattell Press, 1943. $5.00.

This popular treatise on health is based on the latest information and includes thorough discussions of nutrition, sex, infection, inflammation, immunology, mental attitudes and behavior problems. The first three parts are historical. The work is well written and printed with a good type on good paper.

The Hospital in Modern Society. Edited by Arthur C. Bachmeyer, M.D., director, University of Chicago Clinics, and director, Hospital Administration Course, University of Chicago; and Gerhard Hartman, Ph.D., director, Newton Hospital, Newton Lower Falls, Massachusetts. 8°, cloth, 766 pp., with 3 illustrations and 5 tables. New York: The Commonwealth Fund, 1943. $5.00.

In this compact volume will be found a collection of readings selected from the literature in the hospital field and in the allied fields of medicine, public health, management and organization, law, sociology and psychology, comprising the essence of the published material on hospital administration. The work is intended for individuals interested in all aspects of hospital administration, and although not exhaustive, it represents an endeavor to assemble material that is so widely dispersed in the literature that it is unavailable to the average reader.

Gastro-Enterology (in three volumes). By Henry L. Bockus, M.D., professor of gastroenterology, University of Pennsylvania Graduate School of Medicine; and colleagues at the University of Pennsylvania Graduate School of Medicine. Volume II. *The Small and Large Intestine and Peritoneum: Diagnosis and treatment of disorders of the small intestine, colon, peritoneum, mesentery and omentum.* 4°, cloth, 975 pp., with 311 illustrations and 53 tables. Philadelphia and London: W. B. Saunders Company, 1944. $12.00.

This second volume of a complete treatise of the gastrointestinal tract has been published on time despite the great difficulty encountered during the present war. It is hoped that the third volume on the liver, biliary tract and pancreas may be published as promptly.

NOTICES

SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, Boston, on Thursday, December 7, at 4:00 p.m.

FELLOWSHIPS IN CHILD PSYCHIATRY

A limited number of fellowships are being offered for training in extramural child psychiatry. Selection for these fellowships is made by the National Committee for Mental Hygiene following the recommendation of eligible applicants for appointment. These fellows will spend one or two years in a selected clinic, the term and plan of the fellowship to be determined by the peculiar needs of the applicant. The training is pursued according to a definite plan related to the probable future functions of these fellows. Candidates for fellowship award should have had at least a general internship and two years devoted to psychiatry in an approved mental-hospital service, in addition to other qualities fitting them for extramural service. Since this provision of training fellowships comes in response to a definite paucity of personnel in this field, peculiarities of the demand are considered in making appointments. The stipends vary slightly with location and status of the fellow but in general range between $2000 and $2400.

Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. Milton E. Kirkpatrick, National Committee for Mental Hygiene, 1790 Broadway, New York 19, New York.

PUBLIC HEALTH CONFERENCE

The Second Wartime Public Health Conference will be held in the Hotel Pennsylvania, New York City, on October 2, 3, 4 and 5.

Thirteen organizations will co-ordinate their own conferences, demonstrations and symposiums with the seventy-third annual business meeting of the American Public Health Association in discussion and evaluation of all phases of public-health protection that will have far-reaching effects in the postwar world.

New global frontiers in public health will be reported by some of the pioneers who helped establish them. New diseases encountered by American armed forces in various parts of the world, insect problems, control measures against importation of disease by returning veterans and new disinfectants are among the things that will be discussed.

From the civilian front will come reports on sanitary engineering, laboratory technic, milk control, dental care, social and industrial hygiene, school health, public-health nursing, wartime nutrition, wartime food and drug adulteration, air-borne infections and various other diseases.

More than three hundred health officials will read papers or participate in panel discussions. The organizations meeting jointly with the American Public Health Association are as follows: American Association of Public Health Dentists, American Film Center, American School Health Association, American Social Hygiene Association, Industrial Nursing Consultants, Municipal Public Health Engineers, Reciprocal Sanitary Milk Control, State and Provincial Public Health Laboratory Directors, State Directors of Public Health Education, State Directors of Public Health Nursing, State Sanitary Engineers, Teachers of Preventive Medicine and National Publicity Council for Health and Welfare Services.

AMERICAN BOARD OF INTERNAL MEDICINE

The next written examination of the American Board of Internal Medicine will be held on February 19, 1945. The closing date for the acceptance of applications is December 15, 1944.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 28

SATURDAY, SEPTEMBER 30

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, OCTOBER 2

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 3

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, OCTOBER 4

Medicolegal conference, Mallory Institute of Pathology, Boston.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

OCTOBER 3–5. Second Wartime Public Health Conference. Notice elsewhere on this page.

OCTOBER 2–7. Seminar in Legal Medicine, Harvard Medical School. Page 110, issue of July 20.

OCTOBER 3–5. American Public Health Association. Page ix, issue of March 30.

OCTOBER 9–20. 1944 Graduate Fortnight of the New York Academy of Medicine. Page xvii, issue of July 27.

OCTOBER 10. New England Society of Anesthesiology. Page xvii, issue of September 7.

OCTOBER 13. Mental Conditions Resulting from the War. Dr. C. A. Bonner. Pentucket Association of Physicians. 8:30 p.m., Haverhill.

OCTOBER 16–November 3. Third Postgraduate Course in Industrial Medicine. Page xix, issue of September 14.

(*Notices continued on page xv*)